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MULTIPLE MYELOMA *

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To the future understanding of malignancy, present day medicine has made its major contributions in the form of analyses of these conditions into clinical entities; and there has been much of therapeutic advantage in the earlier diagnoses thus made possible. In regard to multiple tumors of the bone, much remains to be accomplished in this direction by a compilation of a more complete series of cases thoroughly studied both clinically and pathologically.

In the present article, multiple myeloma has been selected for discussion from among the multiple tumors of the bone. To the group of thirteen cases (comprising our own series) has been added an analysis of all available cases reported in the literature since 1848—in all, a series of 425 cases. Our work is based largely on the material placed at our disposal by Dr. Joseph C. Bloodgood, in the surgical pathological laboratory at the Johns Hopkins Hospital.

HISTORICAL

Dr. William McIntyre, in reporting the first case of multiple myeloma adequately described in the literature, relates the following:

> Mr. M— a highly respectable tradesman, aged 45, placed himself under my care on the 30th of October, 1845. . . . On taking charge of the case, I had the advantage of meeting Dr. Watson, whom the patient had consulted at the beginning of the preceding summer. . . .
>
> On the 15th (Nov. 1845) Dr. Bence Jones, who had been for some time engaged in examining the composition of the patient's urine, met us in consultation. At his suggestion alum was added to the tonics in use, with the view of checking the exhausting excretion of animal matter. (The animal matter referred to is now known as Bence-Jones bodies.)

The foregoing citation brings together the names of McIntyre, Watson and Bence-Jones, who were jointly responsible for the study of this case. In his report, McIntyre also refers to Dalrymple,[1] who under-

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* From the Surgical Pathological Laboratory, Johns Hopkins Hospital.

1. Dalrymple: Dublin Quart. J. M. Sc. June, 1846.

took the "microscopical examination of the two affected ribs," and communicated his observations to the *Dublin Quarterly Journal of Medical Science.*

The three reports of Dalrymple, Bence-Jones and McIntyre, in the hands of subsequent investigators, were accorded a widely variant degree of attention. Had this been otherwise, perhaps the name of Dalrymple instead of Rustizky (writing twenty-seven years later in 1873) might have been credited with the histologic definition of this disease, and McIntyre instead of Kahler (whose work appeared thirty-nine years later in 1889) cited as the first author to describe multiple myeloma in connection with the excretion of Bence-Jones bodies. Between 1848 and 1873, only three probable cases were added to the literature. These reports were made by Herman Weber in 1867, by Crudeli in 1871, and by Adams and Dowse in 1872. After Kuhne, in 1882, and Stokvis, in 1883, the work of Kahler, in 1889, was responsible for calling attention to this disease.

In Italy, the works of Bozzolo in 1897 and 1898 awakened a series of contributions (over 40 case reports) paralleling the stimulus lent to German clinicians by Kahler's article (followed by some 135 case reports). Although English works must be granted the priority in this field, their contributions have not been so numerous as the German.

Perhaps the best reviews on the subject are to be found in Martiri's article from Italy in the Policlinico and Wallgren's article from Sweden in the Upsala. Rosenbloom, in America, has published a good bibliography of the literature through 1916.

Rather than include a review of the general literature on the subject we have appended, in chronological order, all the case reports which we have been able to compile from a study of the extensive contributions published on this subject. This bibliography gives an historical representation of the progress in this subject and affords to those especially interested an opportunity to check the observations reported here.

ETIOLOGY

Multiple myeloma is essentially a disease of later life, approximately 80 per cent of all cases occurring between the ages of 40 and 70, with the peak of incidence at 55. In this respect, it closely follows other malignant diseases, coinciding almost exactly with the age incidence of a series of 100 cases of metastatic carcinomatous skeletal tumors studied in the surgical pathological laboratory of Johns Hopkins Hospital.

Young adults are not spared, although we have been able to find only five cases occurring in adults under 35. Two of these cases in patients aged 33 and 32 years were not proved microscopically (Anders and Boston). Williams, Evans and Glynn reported one case in a patient,

aged 30; Moore reported one in a patient, aged 27, and Haberfeld and Lordy, one in a patient, aged 22, all three cases being microscopically verified.

Some uncertainty is attached to the occurrence of multiple myeloma in children. Cases reported by Roman (1912) and by Elizalde and Llambias (1913) are not considered myeloma by Wallgren. A case reported by Gilmore (1925) and submitted to the Codman Registry (serial 260) was diagnosed myeloma by Woods and Smith; with Bloodgood, Wolbach and Mallory dissenting. The two cases reported by Berkheiser (1925) resemble the xanthoma variant of the giant cell tumor in one instance, and Ewing's endothelial myeloma in the other. The ages of the children in the various cases reported vary from 2 to 12½ years.

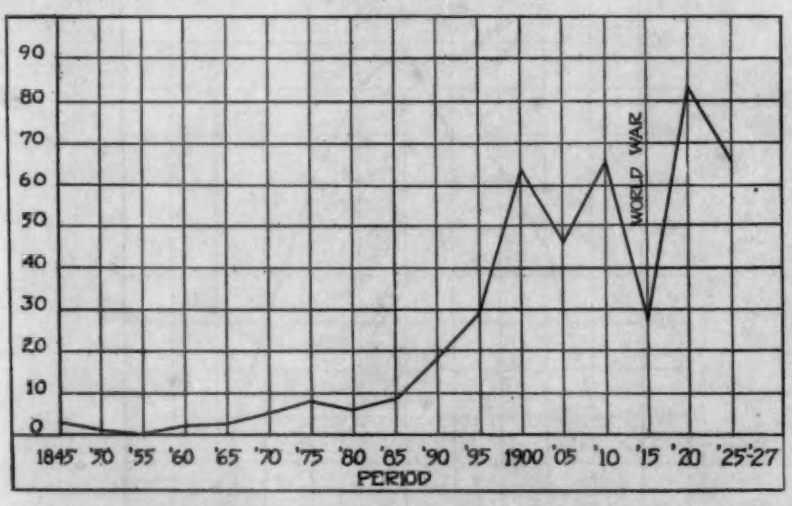

Fig. 1.—Distribution of 425 reports of cases of myeloma by five year periods from 1845 through 1927.

In regard to sex, the occurrence of myeloma in males, roughly estimated, is twice as frequent as in females. Anders and Boston, reviewing thirty-three cases of myeloma, found 80 per cent in males; Wallgren found 68 per cent of males in ninety-eight cases, and in our series of cases, 70 per cent occurred in males.

The occurrence of myeloma appears to be widespread. Reports are numerous from England, America, Germany and Italy. Cases have been described in all parts of Europe—Scandinavia, Russia, Holland, France and Switzerland—in Canada, in Australia and in South America. McCallum and Hamburger have described the disease in a negress, and Jacobson has found it in a Chinaman. The disease apparently does not favor any particular social strata of society, nor does any special climate or region appear to be immune.

Many unsatisfactory attempts have been made to estimate the incidence of myeloma. Symmers and Vance found 3 cases among 4,000 autopsies at the Bellevue Hospital, and in 9,000 autopsies at the Johns Hopkins Hospital there were 4 cases.

We have found myeloma in about 0.03 per cent of all types of malignancy. This incidence is based on life insurance tables in which sarcoma in general is seventh in frequency in the list of malignancy, or 3.5 per cent, with sarcoma of the bone one third of this, or about 1 per cent. Among 400 cases of sarcoma of the bone in the surgical path-

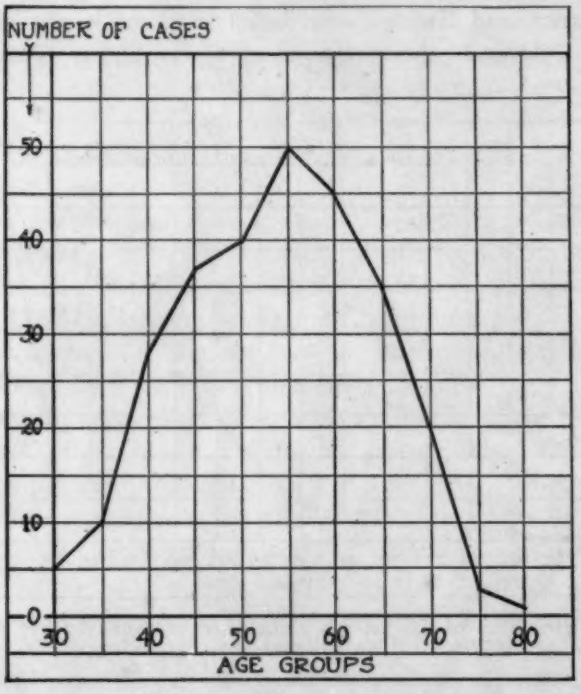

Fig. 2.—Age incidence in cases of multiple myeloma.

ological laboratory at the Johns Hopkins Hospital, 3 per cent were multiple myeloma.

There is little that can be said definitely concerning the actual causative agents of multiple myeloma. Meagerness in the majority of the case reports precludes reliable conclusions drawn from the previous history of these patients.

In isolated cases, some fact in the family history is stressed. The statement by Dornvick that a brother of the patient with myeloma, whose case was reported by Stokvis and Kuhne, died of the same disease, is open to question. Kalischer and Hoffman attributed etiologic significance to a family history of pernicious anemia in their case. In one

of Meyerding's cases, the aunt of the patient had a bone disease with a pathologic fracture of the leg.

With respect to trauma, so much stressed in tumors of the bone, there is more plentiful, if not more convincing, evidence at hand. Although trauma as a factor in the disease was probably not sought for in a considerable portion of the cases, we found it in the history of 20 per cent. When recorded in some cases, it precedes the disease by an interval sufficiently long to render its significance questionable (Hopkins and Savory, Marchand, Funkenstein, Hansen, and our own cases 1 and 10 with intervals of from nine to thirty years). More frequently, the justifiable conclusion is that the trauma was superimposed on a pre-

Fig. 3.—Incidence of multiple myeloma. The white area indicates all types of malignancy, 100 per cent; the area with diagonal lines, all sarcomas, 35 per cent; the dotted area, bone sarcoma, 1 per cent; the solid black area, multiple myeloma, 0.03 per cent.

existing diseased state, since it is of such slight nature that in healthy persons symptoms could hardly have been produced (Wood and Locke, Belden, Osgood, Meyerding, Wallgren and others).

Infection has been cited by some as a suspected causal agent. In patients with myeloma, the combined incidence of influenza, malaria and typhoid is approximately that of trauma. When one considers the frequency of these infections among all classes of patients, however, little remains to be said in regard to their special significance for this disease. Tuberculosis, syphilis, osteomyelitis and infectious arthritis are found associated with myeloma and sometimes coexistent with it. These

diseases, although prone to involve the bone and the joints, are not of great clinical rarity and do not warrant particular emphasis.

From time to time, theories regarding the infectious nature of myeloma have been propounded and the occasional febrile course of the disease stressed. More plausibly, the elevations in temperature can be ascribed to intercurrent infections. All in all, the etiologic obscurity that is attached to malignancy seems to extend in no less degree to multiple myeloma.

CLINICAL CHARACTERISTICS: PAIN

Pain is the outstanding symptom at the onset of myeloma which causes the patient to consult a physician. Although, when its course is viewed in its entirety, the pain is seen to be typical in many of its features, the initial phases are particularly vague and indefinite.

Most frequently the pain at the onset of the condition is characterized as rheumatic. It is wandering and intermittent, but is generally confined to the back. In 70 per cent of the cases the pain is found in the lumbar or sacral regions; in 20 per cent, in the chest over the ribs or sternum; in 5 per cent, in the legs, arms or shoulders, and in 5 per cent, in other parts of the body.

Often the pains are described as neuritic. Girdle sensations, or radiation of pain down the legs is of common occurrence. One of the chief features of the pain is the aggravation of it by motion or pressure. Although subject to remissions, it is capable of acute exacerbations.

It is generally just such sharp accentuations of pain, brought on by sudden movement or muscular exertion, that first calls the patient's attention to the severity of his illness. Most frequently such an unexpected climax of pain is brought about by the strain of lifting a heavy load (Meyerding, cases 10 and 6; Wallgren, Copeland and Geschickter, case 1) or by some inexplicable fall (Devic and Beriel, Cathcart, Bruce, Lund and Whitcomb, and Anders and Boston). These attacks are usually exceedingly severe and leave the patient in a state of prostration and collapse. In case 1 in this paper, the patient was chopping wood, when an overzealous effort precipitated a stroke of pain which felled him to the ground, where he lay motionless for many minutes in a state of utmost pain and anxiety. In a case cited by Kahn, the sudden halting of a train in which the patient was seated, was sufficient to bring on the attack. McIntyre related the incident of vaulting out of an underground cavern, and a consequent prostrating siege of pain. One of Wallgren's patients was overtaken by a seizure when he was going down some steps; he tumbled headlong down the remainder of the flight and sustained a fracture of the radius.

The result of such an attack is to leave the patient for the next few hours or days with bone-breaking pains in the lumbar and sacral regions,

or over the lower ribs. From this stage of relatively intense pain the affliction usually passes over into a period of intermittency, an asymptomatic period which may last as long as several months or even a year. This period in which the malady is apparently arrested is fairly characteristic of multiple myeloma, and it is during this interval of pseudocure that many of the patients have been discharged from the clinics, to fall into the hands of chiropractors and charlatans when the later stages of the disease become manifest.

During the final stages of the disease the pain reaches a climax in which it is at a maximum severity. It is here that portrayals of suffering of the most agonizing sort are to be found in the literature, and it is in this stage that complicating root pains, paresthesia and neuralgia appear.

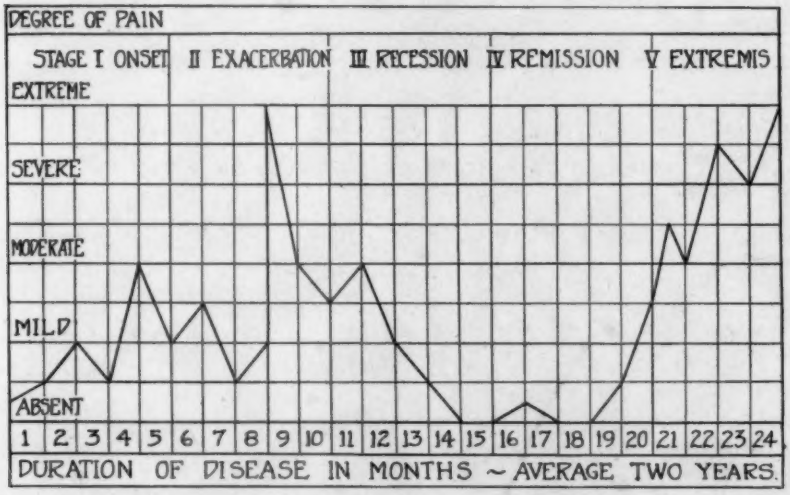
DEGREE OF PAIN
STAGE I ONSET
II EXACERBATION
III RECESSION
IV REMISSION
V EXTREMIS
EXTREME
SEVERE
MODERATE
MILD
ABSENT
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
DURATION OF DISEASE IN MONTHS ~ AVERAGE TWO YEARS.

Fig. 4.—Course of pain in cases of multiple myeloma.

We may sum up the characteristic course of the pains in a more or less composite picture by the following outline:

Stage 1: Intermittent, insidious wandering pains, rheumatic or neuralgic, radiating or girdle in character, worse on motion or pressure.

Stage 2: A dramatic incident of aggravation, with increase of intensity of pain, marked by collapse, prostration and bone-breaking pains.

Stage 3: Subsiding, intermittent pains.

Stage 4: Relative freedom from pain with symptomatic relief.

Stage 5: Recurrent, progressively intense pain, proceeding to death—complicated by neurologic manifestations.

In almost every case studied, the course of pain described here had been manifest in one or more of these stages. Occasionally, the terminal stage only will come under observation, and this will give the appearance

of an acute onset. In over 75 per cent of the cases, however, the course of the disease, while averaging in duration between one and two years, is insidious in its onset.

TUMOR

Not infrequently, tumor formation is the initial symptom that calls attention to the disease.

The distribution of the tumors in cases of multiple myeloma is perhaps the most outstanding diagnostic feature of the disease. The multi-

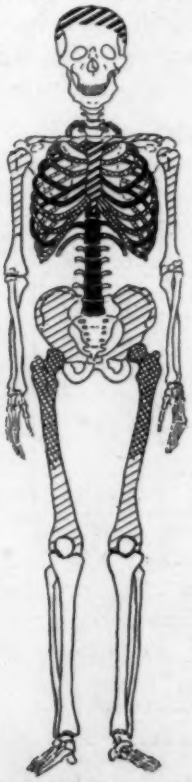

Fig. 5.—Incidence of skeletal involvement according to location. The solid black area indicates the most frequent site; the heavy diagonal lines, the common sites; the checked areas, the fairly common sites; the light diagonal lines, the occasional sites, and the white areas, rare sites.

plicity of the tumors is a cardinal point. In only five cases (Wallgren [case 13], Ewald, Schmorl, Morax, and Geschickter and Copeland) has the disease been found with a single focus, and in all of these cases autopsy was not performed, nor thorough roentgen-ray studies made. There is multiple involvement of the ribs, sternum or clavicles and spine in 90 per cent of all cases. In nine of ten patients with myeloma there is tumor involvement of the ribs, sternum and spine; of the ribs, clavicle

and spine, or of the ribs, sternum, clavicle and spine. Forty per cent of these patients have, in addition, either involvement of the skull or the extremities about the shoulder or pelvic girdles, beside involvement of the trunk. We have not found the extremities alone affected by the tumor in any proved case of multiple myeloma. In rare cases multiple involvement of the spine only, or of the ribs only, has been reported.

Fig. 6 (case 10).—Gross specimen of tumor in the shaft of the femur.

Exceptions are so rare that the statement that myeloma is always multiple and always involves the trunk is practically vindicated. It is confined for the most part to the sites of the red marrow.

The tumors vary in size from that of a pinpoint to that of an orange and more generally from that of a pea to that of a hazelnut. The patient may be made aware of such tumor by tenderness, pulsation, mere lump or pathologic fracture. Occasionally, a diffuse atrophy or so-called myelomatosis may not give evidence of tumor formation (Aschoff,

Boggs and Gutherie, Bomhard, Madsen, Blatherwick, and Wallgren). If the larger tumors are in the sternum, clavicle, ribs or skull, their true nature is probably discovered earlier than when the larger masses are confined to the spine, where they are obscured by mere stiffness or beginning kyphos.

The tumors have been variously described as elastic, yielding, pliable or malleable. Often a parchment-like crepitation may be elicited over

Fig. 7 (case 3).—Gross specimen of humerus showing central location of tumor.

the thin bony shell of the tumor, and where the tumor mass itself is not made out, the bones give the sensation of yielding and fragility. Occasionally, true pulsation may be observed as in the case of Rustizky, or semifluctuation may be made out as observed by Cathcart and Bruce.

Although painless tumors have been described, it is usual, especially in the later stages, for the tumor sites to be extremely painful. The mere touch of the hand, the pressure of a stethoscope or the movement of the bed clothing may be unbearable. The approach of the physician to the bedside is often sufficient to make the sufferer cringe with fear of impending torture.

A peculiar feature of some of the tumors is their tendency to decrease spontaneously in size, with disappearance and reappearance, as in a case cited by Thomas. While roentgen-ray therapy has been known to influence these tumors (Moore), this feature obscures the actual results. Perhaps this variability in size is to be associated with hemorrhage and the absorption of hemorrhage, as, on section, these tumors are frequently exceedingly vascular or hemorrhagic. This quality also explains the occasional pulsating and semifluctuant characteristics.

DEFORMITY

Deformity of the bone has long been recognized (since Kahler) as an accompaniment of multiple myeloma, but its distinctive peculiarities have not been sufficiently emphasized as is evidenced by the frequency with which this disease is confused with Paget's osteitis deformans, osteomalacia and von Recklinghausen's polycystic disease.

In cases of myeloma 60 per cent show thoracic deformity, and in the rarer instances in which this deformity extends to the extremities, it is confined to the regions of the girdle. Bowing of the tibiae as in Paget's disease, marked bending of the extremities as in osteomalacia and globose sites of malunion in the lower limbs that are found in von Recklinghausen's disease practically never occur in cases of myeloma. The deformities are peculiarly thoracic, and their favorite sites are about the sternum and the spine.

At the sternum, in addition to tumor, there is often a sinking in at the angle of Ludwig, or more rarely, a "wavy" deformity of the gladiolus. Parasternally along the ribs and at the clavicles, multiple small tumor nodules may be frequently palpated, and this multiple involvement is so frequent (approximately 50 per cent) that we have termed it the parasternal rosary to call attention to its diagnostic importance.

In the spine, flattening of the lumbar curve, dorsal kyphosis, and actual telescoping of the spinal column due to infraction and collapse of the vertebral bodies occur commonly. In Marckwald's case there was a maximum shortening of 20 cm., while in a case cited by Kahler and one of our own there was nearly an equal amount. Scoliosis is not a rare observation.

These deformities of the trunk lead to a rather characteristic habitus or stance. The patient stands with protruding abdomen, his bulging lower ribs resting on the pelvic brim; his shoulders braced back and his feet set at a wide base to aid in maintaining his equilibrium. Fatigue and pain come on rapidly with standing. The patient walks with the utmost deliberation and caution, if indeed his affliction does not confine him to bed. In some cases, the chin rests continually on the chest, giving rise to decubitus ulcers (Wallgren, P. Weber).

Less commonly, when the skull is involved, there may be interference with mastication. In a case of Anders and Boston the teeth fell out. In Schmorl's case, the skull is reported to have increased 3 cm. in size during the course of the illness—a rare occurrence in cases of myeloma and more typical of Paget's disease.

FRACTURE

The bone destructive nature of the tumors in myeloma is well exemplified by the frequency of pathologic fracture in this disease.

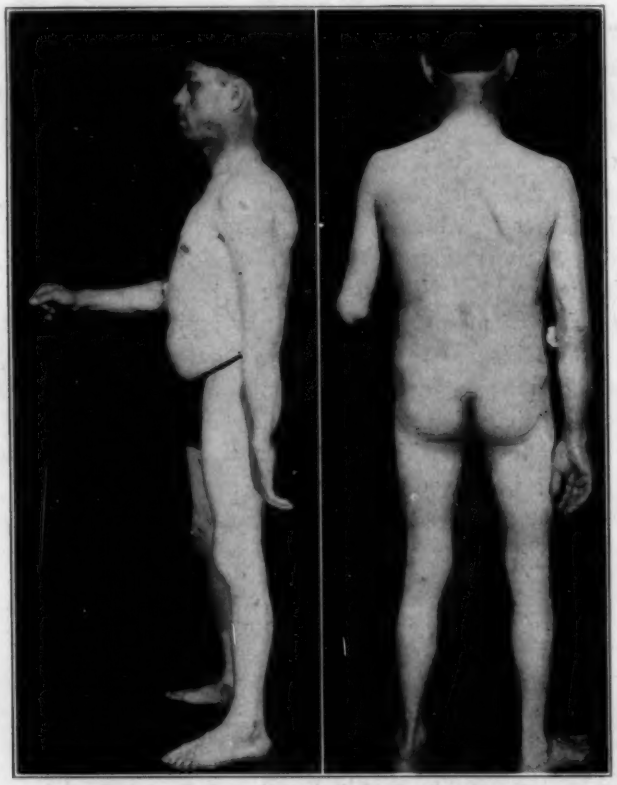

Fig. 8 (case 1).—The stance of a patient with myeloma, showing the protruding abdomen, the approximation of the ribs to the pelvis, the obliteration of the lumbar curve, and the wide base assumed on standing.

Although often escaping clinical recognition, in no other tumor of the bone does fracture occur in so large a proportion of cases.

In his study of pathologic fracture made in the surgical pathological laboratory of the Johns Hopkins Hospital and reported in Scudder's work on fractures, Dr. Bloodgood found an incidence of 38 per cent in cysts of the bone, 25 per cent in multiple myeloma and 21 per cent in metastatic tumors, these three classes of tumors having the highest incidence of fracture.

In a restudy of malignant tumors of the bone, comprising a more recent series of cases in the same laboratory, we have found 33 per cent of pathologic fracture in metastatic tumors of the bone and 62 per cent in multiple myeloma.

While pathologic fracture is not infrequently the source of the first symptom of onset, it is less frequently recognized in itself as an initial sign of the disease. Wallgren's case (case 1) was diagnosed clinically as exudative pleurisy. At autopsy, fracture of the fifth rib was discovered, with a large subperiosteal hemorrhage. In our case (case 1) an early symptom was pain from fracture of the rib, which was only discovered a year later at this clinic by careful roentgen-ray study.

The distribution of fractures in this disease is unique. In other tumors of the bone (as shown by the studies of Bloodgood) pathologic

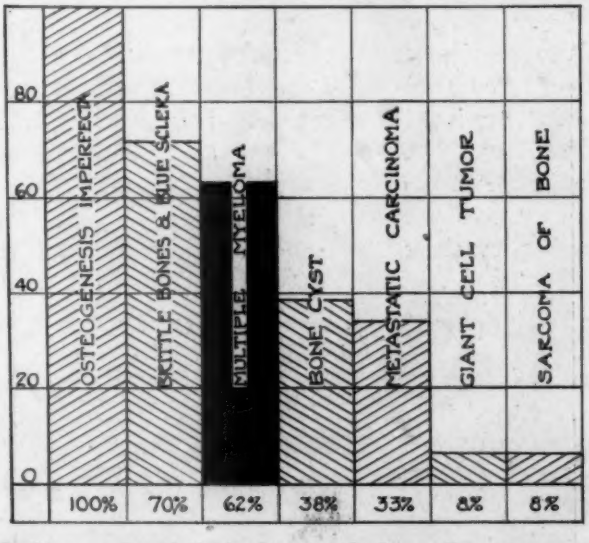

Fig. 9.—Incidence of pathologic fracture in bone diseases prone to fracture, based on 1,040 cases.

fracture occurs almost exclusively in the long bones of the extremities. In contrast to this the principle sites for fracture in multiple myeloma are in the trunk, the prevailing location being the ribs (involved in over 50 per cent of the cases of pathologic fracture in myeloma). The clavicle and sternum are less frequently affected. In two of our own cases the clavicle was involved as it was in the cases of Howard and Crile, Symmers, Moore, Abderhalden and Rostoski, Cathcart, Bruce, Lund and Whitcomb, and Meyerding. Fractures occurring in the sternum are described by Beck and McClearly, Weber, Seegelken, Zahn, Herz, and Williams, Evans and Glynn.

Often a striking feature of the fractures is their multiplicity. Although in other tumors of the bone repeated fractures are often

encountered in the same bone, the occurrence of several fractures in various different bones is exceptional. Not infrequently, however, in cases of multiple myeloma, fractures occur in the same patient in several ribs, clavicle and sternum. Sometimes both lower and upper extremities as well as the thoracic cage are involved (Morse, Hansen, Wells, Symmers and Vance, Osgood, Belden, Gaube, Martiri, Meyerding, Jellinek, Cathcart, Bruce, Lund and Whitcomb, and in our cases 2 and 9).

Fig. 10 (case 3).—Pathologic fracture through the neck of the left humerus. Note the rarified condition of the clavicle and the mottling of the ribs.

Both united and ununited fractures are met with in myeloma. Union of fractures, which is generally slow, has been described by Ellinger, Jellinek, Cathcart and Bruce, Scarlini, P. Weber, Ledingham, and Dialti. In Moore's case, rapid union of the clavicle occurred. In one of Meyerding's cases, in which both femora were fractured, the left united while the right failed to do so.

Spontaneous dislocation of the sternoclavicular joint has rarely been described (Martiri, Howard and Crile). Gradual dissolution of a rib may occur so that the mere pressure of the stethoscope is sufficient to

fracture it, as in a case described by Jellinek. Infraction and crushing of the vertebrae, particularly under strain of lifting, are frequent. The various deformities that arise in this manner have already been referred to.

We think that cases in which fracture is described as preceding the disease as an etiologic factor (Anders and Boston) are subject to reinterpretation. There is no evidence at hand to substantiate preceding fracture in healthy bone as an etiologic factor in multiple myeloma, as has occasionally been demonstrated for giant cell tumor and sarcoma of the bone.

PULMONARY CHANGES

When the thoracic deformity of patients with multiple myeloma is marked, chronic bronchitis and emphysema are of common occurrence, averaging 55 per cent of the cases. The prevailing type of bronchial involvement is a diffuse persistent bronchitis of the mucopurulent variety, characterized by a productive or hacking cough. The debilitated and cachectic condition of these patients, the hypostatic pulmonic changes dependent on their bedridden state and the restricted alveolar ventilation brought about by painful respiration may be considered contributory factors to this bronchial involvement.

Second to bronchitis, emphysema is most frequently observed (Wallgren in five cases, Morse in two cases, McIntyre, Bence-Jones and Dalrymple, Ellinger, Weber and others). Dyspnea and asthmatic attacks are often accompanying features. In these cases, the anginoid pains particularly emphasized by such violent expiratory efforts as sneezing and coughing, cause the patient to breathe shallowly with the chest held in a distended inspiratory state. Weakening of the alveolar walls consequent on nutritive changes makes emphysema a likely possibility.

Various forms of pleurisy have been reported by Senator, Sternberg, Herz, Caccini, Warstat, Kahn, Vance, Wells, Symmers, Morse, Austin, Beck and McClearly, McIntyre and Wallgren. In some cases, this has been described as fibropurulent (Herz), and occasionally as an empyema (Hansen, Oftedal). At autopsy, subpleural nodules or indented fracture deformities of the ribs have been found in association with the pleuritic changes. Pulmonary tuberculosis has rarely been reported in patients with myeloma (Kahn, Austin, Wallgren).

In these various conditions of the lung, there is a fatal progression—generally onward to a terminal pneumonia.

NEUROLOGIC OBSERVATIONS

Attacking the bony framework, which otherwise serves as a natural defense for the nervous system, the tumors of myeloma soon manifest themselves by an ensemble of neuralgic and neurologic symptoms. The most important of these is the paraplegia that follows the involvement

by the tumor of the vertebral column. This together with other forms of neural disturbances is found in about 40 per cent of the cases.

The paraplegia that develops is due to compression of the spinal cord by vertebral tumors most frequently located in the lower dorsal or the lumbar region. The onset is usually insidious, marked at first by weakness of the legs with a tendency to stumbling. There is dwindling sexual appetite, hesitancy in starting the flow of urine and diminished epicritic sensation over the lower extremities. In the next stage, there is exaggeration of the reflexes with development of a positive Babinski sign and ankle or patellar clonus.

In the final stage, there is a flaccid paraplegia with incontinence and the development of decubitus ulcers. The involvement will rarely be unilateral (Meyerding, case 6). In an unusual case reported by the same author (case 9), paraplegia came on after a fall and then gradually disappeared. In a case studied by Bertoye, there was a paralysis that recurred after temporary cessation. These rarer forms of receding neurologic involvement parallel the occasional regressive changes seen in the tumors of the bone in cases of myeloma and are related to vascular changes in the spinal tumor.

In a smaller percentage of the cases, the diverse involvement of the skeleton gives rise to neurologic symptoms in other regions. In cases reported by Bloodgood, Anders and Boston and Hammers, diplopia developed. In Meyerding's third case, anisocoria and failing vision accompanied a tumor of the skull. In a case of Herz, paralysis of a hand was present. In Senator's case, glossoplegia with partial laryngeal and pharyngeal paralysis developed, and Stokvis found difficult deglutition in his patient. There was decided alteration of the voice in a case studied by Anders and Boston.

Wallgren and also Venturi reported cases with tumors in the skull giving rise to thromboses in the intracranial sinuses. In Venturi's case, there was thrombosis of the central artery of the retina with complete blindness. Diminution of vision was present in Askanazy's case.

Not rarely tumor masses of the ribs give rise to intercostal neuralgia and paravertebral tumors to radiculitis with severe lightning-like root pains. Such involvements are sometimes complicated by herpes zoster (Conti, Anders and Boston, Bomhard, Wallgren, and our case 1).

Senator and others, lacking definite anatomic proof that direct impingement by tumor is responsible for many of the lesions of the nerves already described, ascribe to them a toxic origin. Evidence of tumor, however, is almost always found in the region of the neurologic symptoms, which would not necessarily be so were a circulating toxin the agent responsible for these disturbances. Ginsburg,[2] in describing

2. Ginsburg: Hodgkins Disease: With Predominant Localization in Nervous System, Arch. Int. Med. **39**:571 (April) 1927.

neurologic disturbances of a similar nature, observed clinically in ten cases of Hodgkin's disease, is of the opinion that they were due to direct invasion of the nervous system by the proliferating tissue.

Although the psyche remains clear in most instances, terminal confusion and coma are not rare. Occasionally, cases of myeloma occurring in psychiatric patients have been reported (Wallgren).

NEPHRITIS

The changes in the kidney in cases of myeloma are as varied and diverse as the pulmonic changes, and are present in a larger portion of the cases (70 per cent).

Hammond [3] is of the opinion that a chronic nephritis with nonprotein nitrogen retention and a low blood pressure is typical of multiple myeloma. While we have been able to find four such cases (Meyerding, two cases, Grant and Brewer, and one of our cases), we have also found nephritis with nonprotein nitrogen retention and hypertension in two of our own cases (165 systolic and 105 diastolic and 158 systolic and 108 diastolic). Blood pressure determination in connection with blood chemistry studies are reported rarely enough to make any conclusions on this point hazardous. It is true that blood pressures in general are low (from 110 systolic and 60 diastolic to 130 systolic and 80 diastolic), but we have been able to collect readings in only some thirty cases.

Clinically, the usual occurrence is nephritis of the chronic type, although in case 1 of our series the patient dated the onset of his symptoms from an attack of acute nephritis with chills and fever, anasarca, throbbing headache and hematuria. On admission, his nephritic symptoms were of the chronic hypertensive, nonprotein nitrogen retention type. Gottardi described a similar case which began with intermittent hematuria.

In other cases (Wallgren and our own series), the original clinical diagnosis of the patients' underlying condition was chronic nephritis with cardiac hypertrophy. In some cases, changes of the eyeground are reported (Anders and Boston, Ellinger, Massini). In most instances, the report of nephritis is based on autopsy observations. In half of the cases, the nephritis was described as sclerotic or interstitial, and in about one third as parenchymatous. Moore and also Wallgren have reported cases diagnosed as nephrosis—or tubular nephritis, and H. Weber, Jochmann, and Schumm, Rosen and Bach, Senator and others have reported the amyloid reaction in the kidneys.

In twenty cases, paraplegia and nephritis are reported in the same patient. In some cases, the nephritis definitely preceded the paraplegia;

3. Hammond: South. M. J. **17**:483, 1924.

in other cases, the paraplegia was the underlying condition with urinary retention and an ascending infection giving rise to cystitis, pyelitis and renal abscess. In our seventh case, the urinary infection followed paraplegia and could be ascribed to the use of a retention catheter.

Metastases (Froenkel, Morse, and our case) have more rarely been demonstrated in the kidney.

Great interest is attached to the association of nephritis and Bence-Jones bodies in cases of multiple myeloma. This occurs frequently and we found both in ninety-two cases, as shown in figure 11.

Decostello, by injection of Bence-Jones bodies into dogs, concluded that a previous nephritis was necessary to their excretion. Stokvis, on

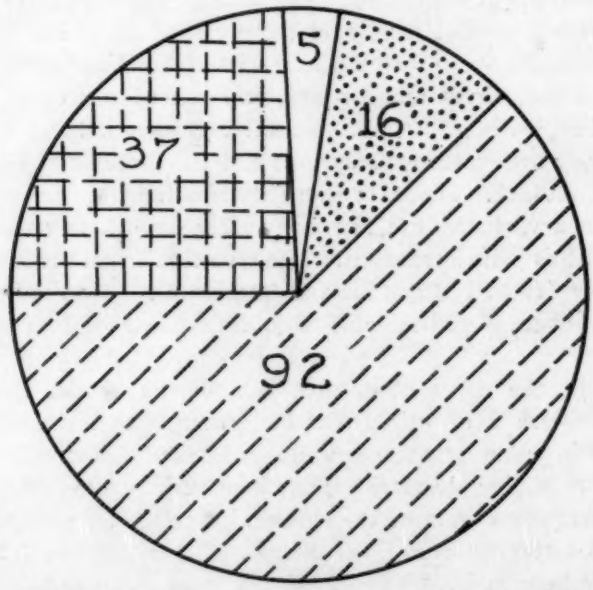

Fig. 11.—Nephritis and Bence-Jones bodies in 150 cases of myeloma. The white area (3.3 per cent) indicates an absence of nephritis and Bence-Jones bodies; the dotted area (10.7 per cent), Bence-Jones bodies only; the crossed area (24.6 per cent), nephritis only and the area of broken lines (61.4 per cent) nephritis and Bence-Jones bodies.

the other hand, claimed to have induced nephritis in these animals by similar injections of Bence-Jones bodies. Longcope's work on the effects of foreign protein on the kidney in man would seem to support the contention of Stokvis, that nephritis might thus be brought about.

No single theory for the origin of nephritis has a monopoly on the evidence at hand. While in some cases Bence-Jones bodies are reported in the urine without the ordinary albuminuria expected with foreign protein shock to the kidney, still it is possible that by repeated damage to the kidney a dysfunction is brought about.

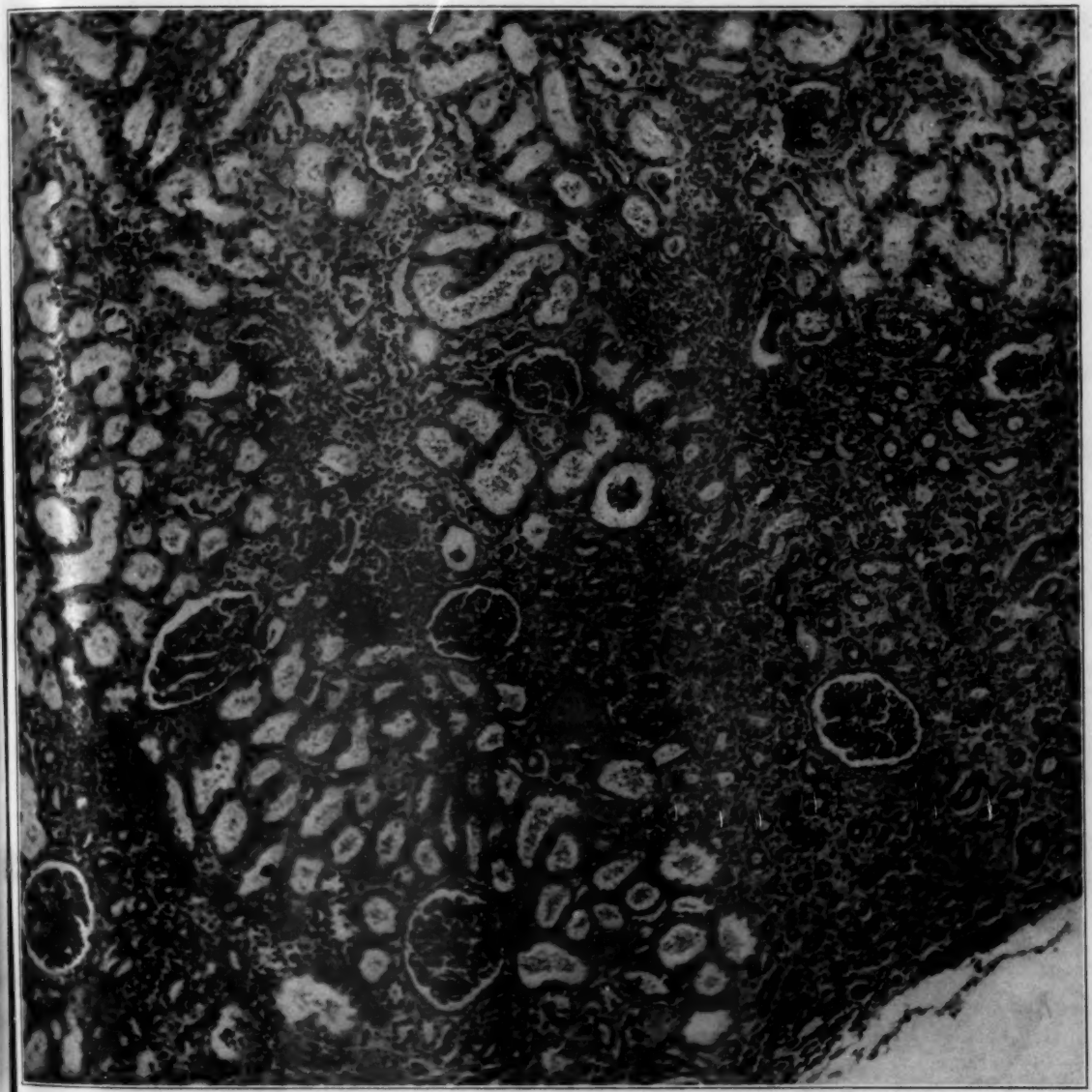

Fig. 12 (case 7).—Pathologic changes in the kidney. The urine showed two plus albumin, casts and blood cells. The phthalein excretion was 40 per cent for two hours.

GASTRO-INTESTINAL SYMPTOMS

In a disease running a fatal course, many terminal complications are to be expected, and certain of the gastro-intestinal symptoms of patients with myeloma are apparently on this basis. The diarrhea often met with and the colicky pains described (Meyerding, Wallgren, Wright, Austin, Bozzolo, Bertoye) are associated with the conditions found at autopsy in most instances of enterocolitis, which, as MacCallum has pointed out, is often a terminal complication in patients with nephritis.

The fatal hematemesis in Bertoye's case, the melena in Wallgren's case 11, and the epistaxis not infrequently observed (Anders and Boston, Bertoye, Kriebich, Hoffmann, Bradshaw and Warrington, and in some of our own cases) likewise may be regarded as terminal manifestations associated with a lowered platelet count in marked anemia (as pointed out by Naegeli).

There is an occasional case of outspoken peptic ulcer (Vance, P. Weber, Wallgren), however, which is more difficult to explain. Gastric analyses have been done in only rare instances (Wallgren, McConnel, and our own cases). These determinations, with few exceptions, show an absence of free hydrochloric acid. To complicate the picture one step further, metastases or extensions of the tumor to the stomach and duodenum have been reported in cases of Renzi, Martelli and Morse. Ulcer formation has not been correlated with tumor formation in these rare instances.

The most frequent gastro-intestinal symptoms are nausea, vomiting and colicky pains. In some cases, there is vomiting without nausea. In cases reported by Meyerding, Wallgren and Jacobson, and in our own series, these gastric disturbances have been associated with compression of the spinal cord, and were perhaps analogous in some way to the gastric crises found in tabes dorsalis (as suggested by Martiri).

The various types of gastro-intestinal symptoms already mentioned represent about 20 per cent of the cases.

METASTASES

It was long thought that multiple myeloma never involved the internal organs by metastases, and that if metastasis occurred, it was merely as a spreading from one bone to another of a tumor growth primary in a single focus or an original group of foci. Direct extension to surrounding parts was conceded, but when tumor growths were found in the liver and spleen, Lubarsch sought to explain them as separate nodules in hemopoietic tissue, arising independently rather than by metastases.

Actual metastasis to internal organs, however, is not at all rare when a careful review of cases has been made. The spleen has been reported as the site for metastases in cases by Arnold, Aschoff, Madsen,

Rioch, Versé, Askanazy and Reach. Hoffmann, Mieremet, Schule, Herzheimer, Shennan, Arnold, Madsen, Kudrewetsky have reported metastases in the liver. Growths in the lymph glands were reported by Arnold, Christian, Lubarsch, Lunghetti, Charles and Sanguinetti, Harbitz, Funkenstein, Devic and Beriel, Mieremet, Schule, Herzheimer, Sternberg, P. Weber and Bechtold.

More rarely, other organs are affected, the tonsils (Shutz, Anders and Boston), the thyroid (Fraenkel), the suprarenals (Bechtold), the ovaries (Herrick and Hektoen) and the meninges (Krudrewetsky).

The metastases, microscopically similar to the original tumor, are of the same circoid formation in the gross, but rarely attain a large size (size of a walnut is the largest). When found, they are generally multiple, unless apparently arising by extension from proximal bone.

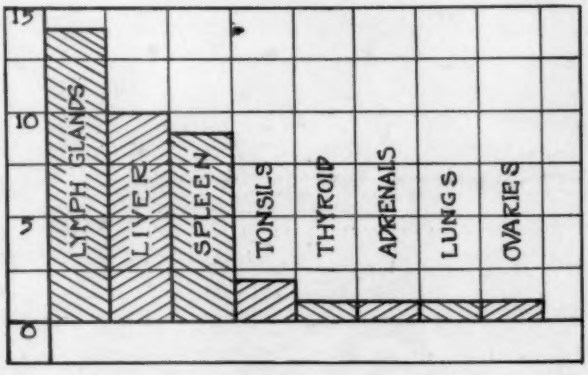

Fig. 13.—Sites of metastases in cases of myeloma. The left hand column shows the number of cases.

In general, pulmonary metastases are not found in myeloma. From the point of view of roentgen-ray diagnosis this is exceedingly helpful. The occurrence of subpleural extension of the tumor can be differentiated with due care, and actual metastatic growths occurring in the lungs have been reported only by Wieland.

Usually the hemopoietic tissues are the favorite site for the spread of the tumor—the spleen, the liver and the lymph glands predominating. Microscopically, in the bone marrow growths, free tumor cells have been found lying within the blood vessels (Dubos, Abrikosoff, Hoffmann, Gluzinsi and Reichensteink, Kyjukoff, McCallum, Shennan, Saltykow, Schwartz, Perman, Wielland, Weinberg, and others [fig. 15]). This has been cited by certain authors to explain the origin of the metastases.

BENCE-JONES BODIES

Repeated statements in the literature cite the incidence of Bence-Jones bodies as 80 per cent for all cases. Search for the authority or

evidence for this statement failed to disclose its source. In the present study, excretion of these bodies was reported in 65 per cent of all cases.

On the other hand, a search for an albuminoid substance in the urine of patients with diseases other than myeloma, although infrequently carried out, has shown this substance to be present in a widely variant group of bone and bone marrow diseases. In 107 cases of diseases other than multiple myeloma in which we could find (either in the literature or in the surgical pathological laboratory of the Johns Hopkins Hospital) a record of a determination, Bence-Jones bodies were found in twenty-six cases. Most of these tests, of course, were made on patients suspected of having myeloma, and the results throw some light on the value of the test in differential diagnosis.

TABLE 1.—*Bence-Jones Bodies Found in the Urine of Cases Other Than Multiple Myeloma*

Disease	Reference	No. of Cases
A. BONE DISEASES		
Metastic tumors of the bones	Orrum, Bradshaw, Boston, Boggs and Guthrie, the authors	9
Multiple sarcoma of the bones	Seegelken, Gilmore	2
Senile osteomalacia	Rascke	1
Polyfibrocystic disease	Groves	1
Comminuted fracture	Campbell with Horsfall	1
Caries of the spine	Wallgren (cited)	1
Tumor of the jaw	Fitz	1
	Total	16
B. BLOOD DISEASES		
Lymphatic leukemia	Herz, Frohman, Decastello, Askanazy	4
Myelogenous leukemia	Simon, Moore, Authors	3
Chloroma	Weinberger	1
Polycythemia	Pribram	1
Experimental aplastic anemia (in a dog)	Zeulzer	1
	Total	10
Total, all cases		26

Table 1 has been compiled from the literature and from cases in the surgical pathological laboratory of the Johns Hopkins hospital.

Despite the fact that twelve different conditions are enumerated in the foregoing table, the striking feature that all of these diseases involve either the bone or bone marrow is well emphasized. In the case of Fitz, so often cited as an example of Bence-Jones bodies in myxedema, actual perusal of the reference showed the patient to have a tumor of the jaw with sequestra in addition to the hypothyroid symptoms. The case of Coriat in which these albuminoid bodies were found only in the pleural fluid has been referred to by some as miliary tuberculosis, by others as multiple sarcomas. Coriat, in reporting the case, did not describe symptoms of either, contenting himself with remarks concerning the rare and obscure nature of the patient's condition. The evidence would, therefore, seem to indicate that the excretion of Bence-Jones

bodies in the urine is specific not for multiple myeloma, but for some pathologic process located in the red marrow bones.

The demonstration of Bence-Jones bodies in the urine depends on the appearance of a white cloudy precipitate between the temperatures of 50 and 60 C. (sometimes as low as 43 and 46 C.), and on further heating, this precipitate goes into solution at about boiling (90 and 100 C.). On cooling, the precipitate reappears. In some cases in which the precipitate does not clear on boiling, the addition of a few drops of acetic acid (5 per cent) will dissolve the turbidity. If serum albumin is present in the urine, a few drops of acetic acid should be added, the serum albumin coagulated and filtered off at boiling, and the foregoing procedure then carried out.

Although various workers claimed to have obtained a substance resembling Bence-Jones bodies from various tissues of patients with myeloma (Jacobson from the blood, Ellinger from ascitic fluid, Martiri from the ribs, etc.), the exact source and significance of the substance have never been proved.

It should be borne in mind, in testing for these bodies in patients with myeloma, that they usually appear late in the course of the disease; at first they are present only intermittently, and generally are a constant occurrence only in the terminal stages.

THE BLOOD IN MULTIPLE MYELOMA

In cases reported as myeloma all types of blood pictures have been described ranging from primary or secondary anemia to polycythemia, and from leukopenia to leukemia.

When proved cases only are included in the tabulation, those with the blood picture of a leukemia can be set aside under a diagnosis of pseudoleukemia or chloroma. The one case of polycythemia with a red blood cell count of 9,000,000 and a hemoglobin of 102 per cent is not a proved case, although Bence-Jones bodies were found in the urine, tumors were shown by roentgen-ray examination in the sternum and ribs and there was pathologic fracture of a rib with pleurisy and nephritis. Pribram, himself, was at a loss as to how to classify the case, and unfortunately biopsy was not obtained.

In seventy cases of multiple myeloma with complete blood counts, there was a red blood cell count of over 4,000,000 in only 16, or 23 per cent, so that it can be safely said that the predominant picture is that of an anemia. The greater number of patients have an anemia ranging between 2,000,000 and 3,000,000 red cells as will be seen from figure 14. In only three cases is there an anemia of the primary type with a high color index and a leukopenia, although in twenty-six cases there is a high color index.

Normoblasts have been reported in some cases (Austin, Christian, Thomas, Ellinger, King, our cases, and others) and megaloblasts have

occasionally been found. There is the usual anisocytosis and poikilocytosis found in a marked anemia.

The white blood cell count and its differential count present certain peculiarities. In 100 white blood cell counts 70 per cent of the cases are within normal limits; 23 per cent show leukocytosis and 7 per cent a leukopenia. The majority of the cases in which there is a leukocytosis range in counts from 11,000 to 15,000. In this respect there is no peculiarity, for we would expect to find leukocytosis in patients who so generally suffer from secondary infections.

The unusual features occur in the differential count. In about sixty cases with complete differential count, myelocytes ranging between 1 and 10 per cent were found in fifteen cases and eosinophils ranging

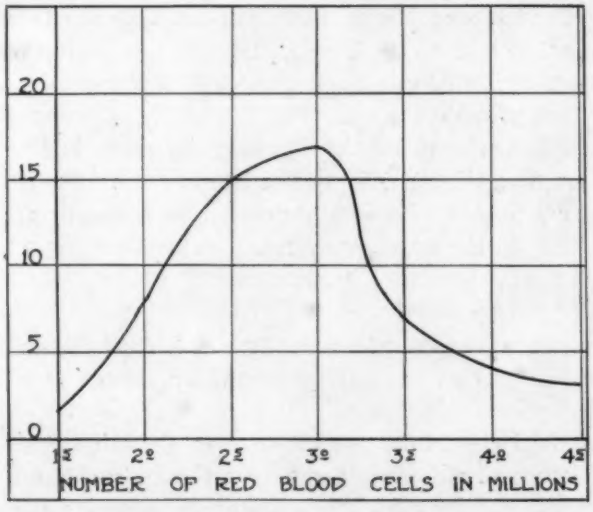

Fig. 14.—Red blood cell counts in 70 cases of myeloma. The left hand column shows the number of cases.

from 3 to 5 per cent in five cases. Vaughn,[4] has reported myelocytes as a common occurrence in cases of advanced carcinoma, an interesting point in this connection. Abnormal mononuclears or Turk's irritation phenomena were found (the authors, Wallgren, Weinberg, Schwartz and others). In general, there is a tendency for the mononuclear elements to increase, a relative lymphocytosis not rarely being present. In some cases, the tumor cells have been reported circulating in the blood (Beck and McClearly, Ruszinsky and Reichenstein, Aschoff, Weinberg and Schwarz, Stumm, Wallgren and Aschoff). The exact identity of such cells, however, has not been established. An occasional case of malignancy with tumor cells in the circulation has been reported for other

4. Vaughn: Operable Cancer, J. A. M. A. **69**:1952 (Dec. 8) 1917.

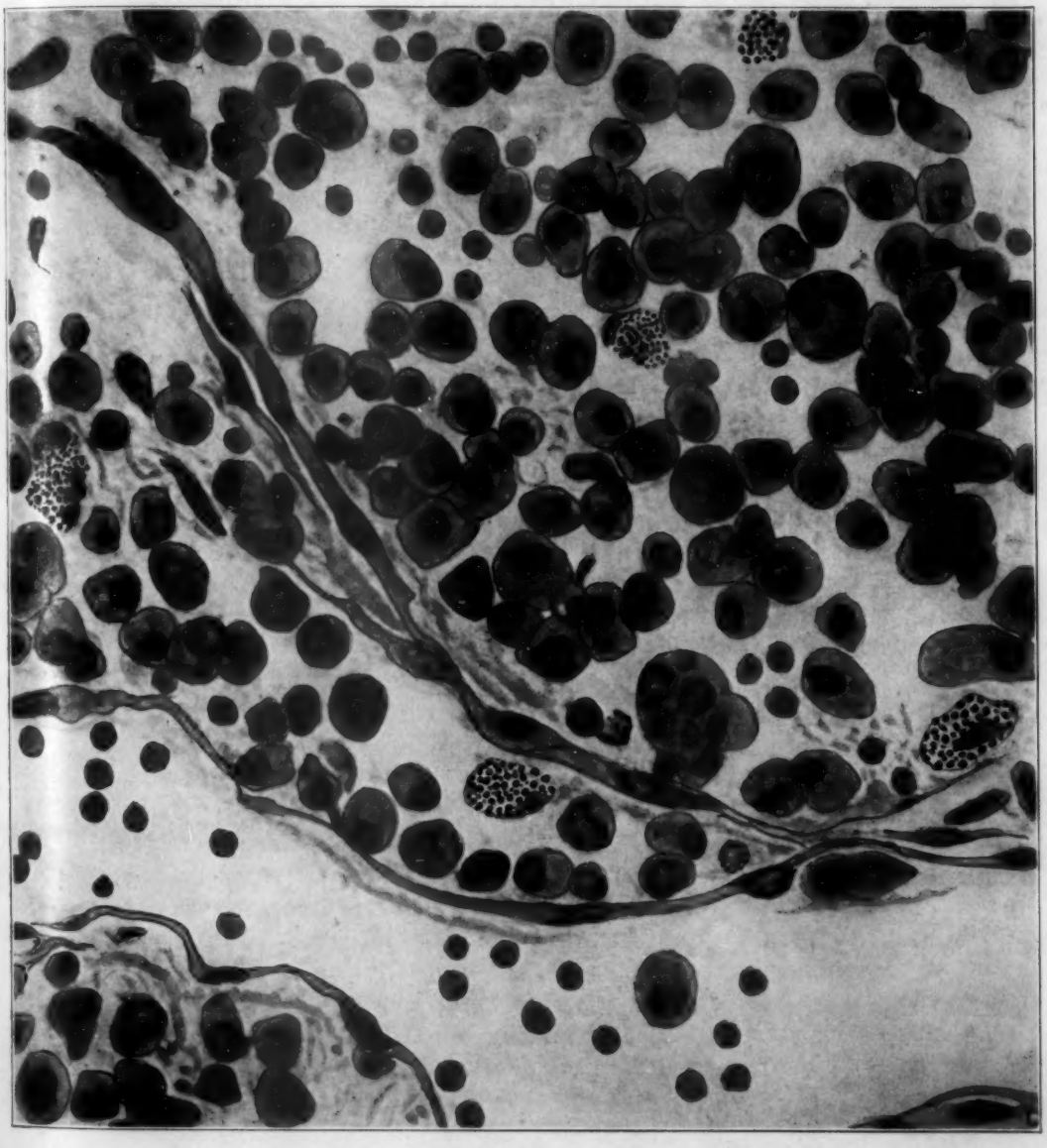

Fig. 15 (case 9).—Myeloma cells in the small blood vessels. The photograph has been retouched to show accurately the chromatin arrangement in the nuclei, the presence of multiple nuclei cells and eosinophils.

diseases (Schleip in gastric carcinoma with vertebral metastases, Marcus Quennell in sarcoma). In view of the fact that myeloma cells can be found in the vessels pervading the tumor areas, such occurrences are not remarkable.

As a group, these cases present rather remarkable conditions in their blood picture. The high hemoglobin in 38 per cent of the cases is contrary to the ordinary secondary anemia of malignancy, nor is there the aplastic type of anemia bespeaking widespread bone marrow disease, which one might expect. The normoblasts and megaloblasts typifying regeneration, and the eosinophils are also contrary to what one would expect. The absence of leukemia is not suggestive of a tumor of hemopoietic tissue.

The condition is complex. In some cases, there is a tendency for a displacement of hemopoietic tissue by tumor elements with consequent anemia simulating the primary type. On the other hand, in the more chronic cases, a course resembling malignancy may give rise to an anemia of the secondary type. Either of these two conditions may gain the ascendancy, and this gives the blood picture of multiple myeloma a variable character.

ROENTGEN-RAY OBSERVATIONS

When complete roentgen-ray studies are made of the patient with myeloma much is generally to be found that is typical of the disease and helpful in making a diagnosis.

The changes taking place are characteristically distributed in the trunk, in the sternum, in the ribs and in the spine. The skull is not rarely involved, and when the long pipe bones are affected, there is a tendency for the tumors to be located about the pelvic or shoulder girdles, not infrequently affecting the pelvis. The lesions are characteristically multiple and, in general, confined to the location of the red marrow, and thus in the roentgenogram may be termed typically central.

The tumors themselves are bone destructive and frequently show up in the pictures as rounded, punched-out areas varying from the size of a pea to that of an orange. Sometimes they are more diffuse, giving a rarefied osteoporitic appearance to the roentgenogram, or, when multiple areas have become confluent, resembling mottling.

In the thoracic cage, the ribs are most frequently diffusely mottled, but at the site of the ossified costochondral junctions, there is a tendency for the tumor nodules to stand out more distinctly as areas of bone absorption. Not infrequently, tumors about the size of an almond are to be seen lying on the ribs, rather than appearing centrally. At autopsy, they can be found projecting inwardly as subpleural nodules.

Pathologic fractures occur most frequently from the fifth down to the twelfth rib. The break is generally not a clean one, but a default through a widened and rarefied area of rib, easily overlooked. In some

cases, although there are noticeable fracture deformities, there is not the extreme bending seen in osteomalacia or the multiple globose enlargements and distortions seen in von Recklinghausen's disease at the site of repeated fractures.

The clavicles are most frequently expanded and rarefied at either the sternal or acromial ends. They are sometimes fractured or subluxated at the sternoclavicular joint. In the sternum, unless lateral views are taken, involvement of this bone may be mistaken for mediastinal shadow when the tumor is sufficiently large (Lubarsch, Verebely, Permin).

Rarefaction and globular tumor formation are both to be found in the spine. Asymmetrical spheroid tumor formation of a vertebral body

Fig. 16 (case 7).—Roentgenogram of the thorax showing tumor nodules along the ribs and pathologic fracture of the seventh right rib. Most of the lower ribs show rarefaction and deformity.

may be seen in figure 17. In the rarefied vertebra, infraction and collapse lead to shortening, disappearance of the intervertebral disks and twisting of the spinal column with scoliosis. Involvement is most frequent in the lower dorsal and lumbar regions, There is a tendency unlike metastatic carcinoma for more than one vertebra to be involved.

When tumor formation is found in the skull, the roentgenogram is of great diagnostic value. Unlike the typical furry thickness of the skull seen in Paget's disease and sarcoma and sometimes in metastatic carcinoma from the prostate, there is no increase in the width of the tables, as a general rule. Multiple punched-out areas are found confined mainly to the frontal and upper parietal regions, generally not as large as in cases of metastatic carcinoma or as mottled as in advanced

cases of syphilis of the bone. Large frontal sinuses somewhat like those found in cases of acromegaly have been observed in three or four cases. This is in contrast to the condition found in Paget's disease and leontiasis in which the size is decreased.

The pelvis is sometimes affected together with the rest of the skeleton, giving the impression that the bone is bloated or puffy, with an attenuated structure like edematous tissues.

Fig. 17 (case 1).—Roentgenogram of spine showing compression of vertebra, and nodular tumor formation of the lumbar vertebra.

When the long bones are affected, they show, in the early stages, either the multiple punched-out areas, or more rarely an expanded cystic change. Sooner or later, however, they assume an attenuated appearance, in which there is a general rarefaction, rather than expansion within a shell.

Some formation of bone occurs, as is proved by the healing of pathologic fractures and by microscopic examination, yet the roentgenogram rarely substantiates the formation of new bone in the reviewed cases. Harbitz and also Schmorl, however, have described what they term sclerosis occurring in the skull and in the long pipe bones some distance from the area of bone absorption.

MICROSCOPIC

As in other malignant conditions, the last resort in diagnosis in multiple myeloma is biopsy. Cutting down on the tumor one finds a

Fig. 18 (case 1).—Roentgenogram of skull showing rarefaction and tumor involvement of the parietal and frontal bones. Note the large frontal sinus.

bone shell of parchment-like thinness, which cuts readily with the knife. Sometimes the cortex is entirely resorbed and the spongiosa rarefied. The tumor often bleeds freely and is composed of a dark red or gray red mass of gelatinous tumor, the color varying according to the vascularity. Very rarely, cells that have infiltrated about the periosteum will give rise to distinct extraskeletal tumors (Wallgren, cases 6 and 7).

When cases are selected for study the diagnosis of which rests on a thorough clinical basis, the microscopic observations are generally uniform. The majority of cells in myeloma are round, oval or egg-shaped, 9 to 11 mu in size, with an eccentrically placed nucleus averaging 4 or 5 mu. Not rarely, a cell containing two or possibly three nuclei is seen, and in

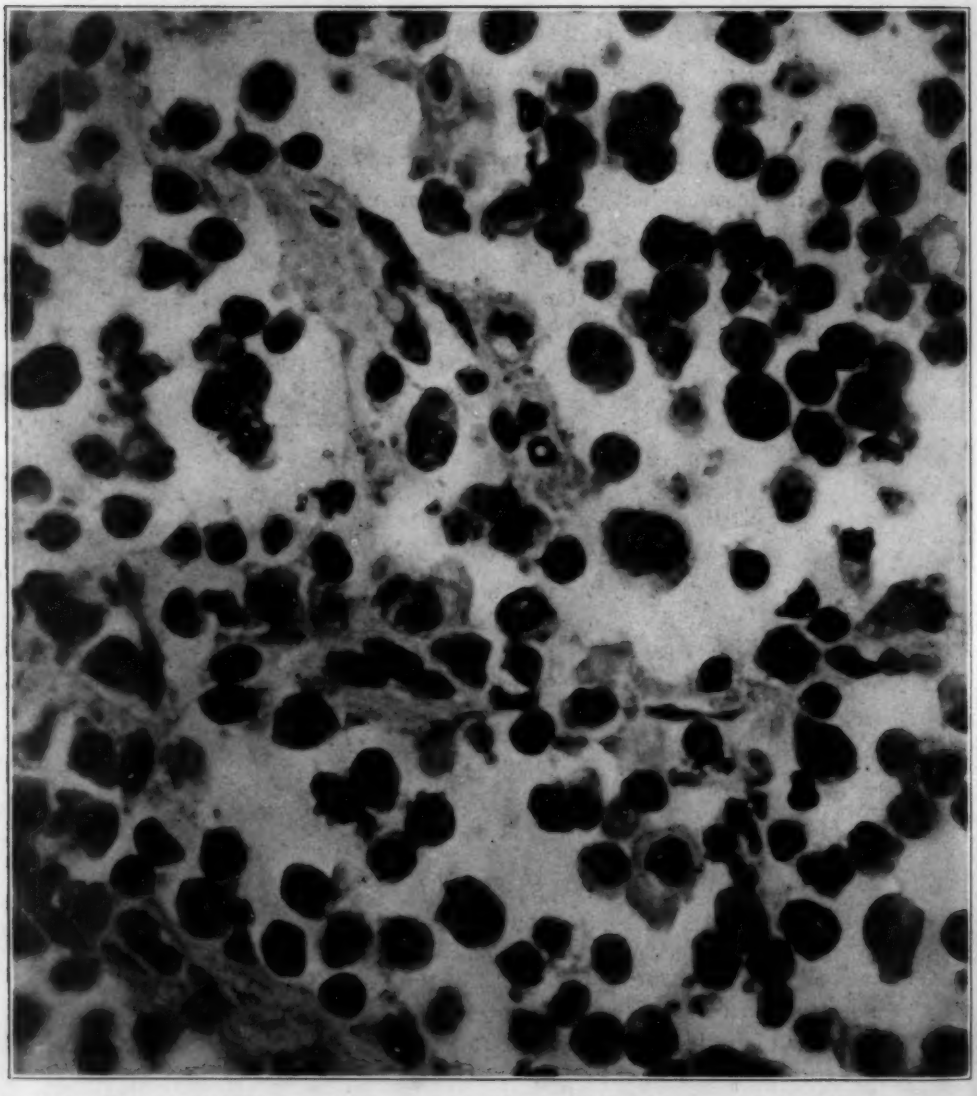

Fig. 19 (case 2).—Typical plasma cell type. Note the uniformity of chromatin arrangement in the nuclei.

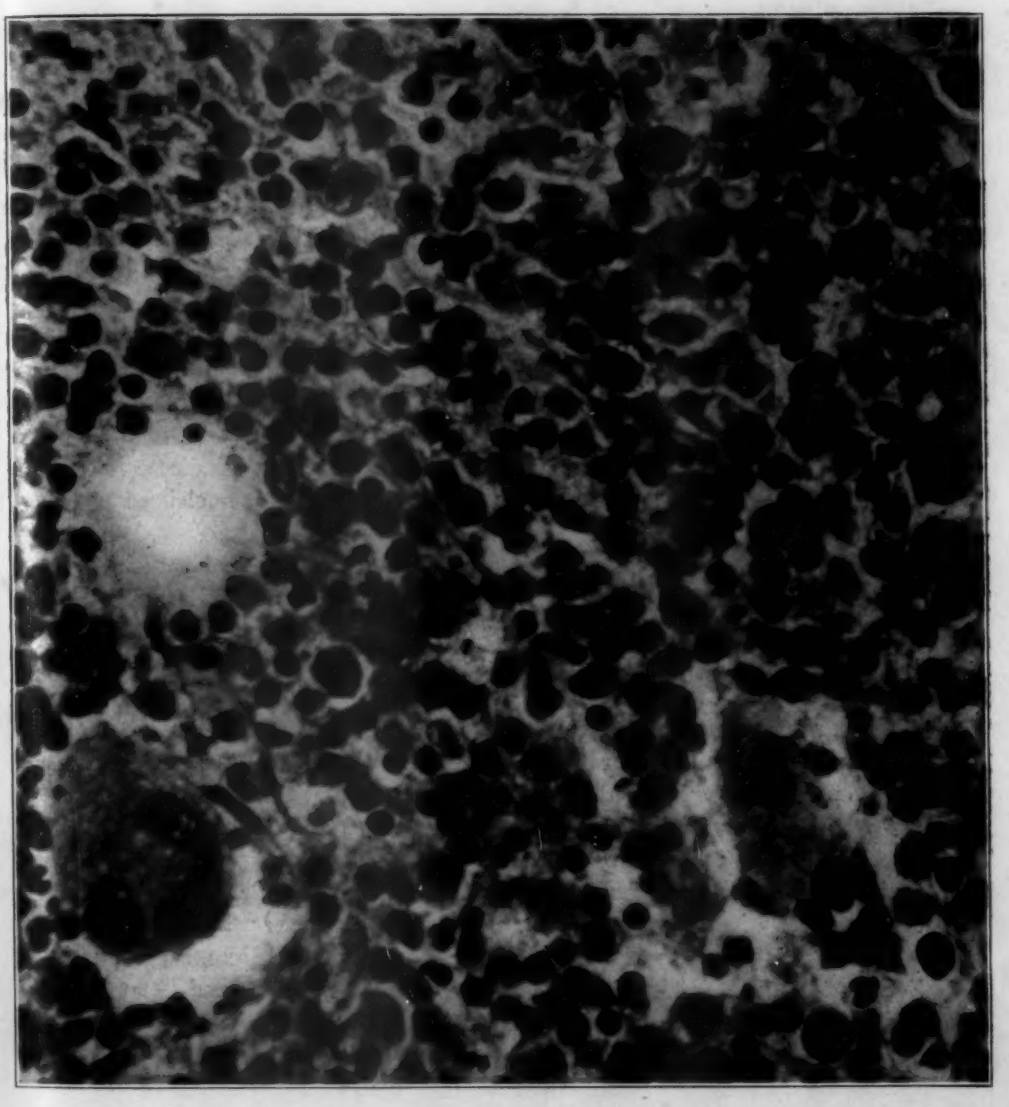

Fig. 20 (case 3).—Photomicrograph stained with polychrome methylene blue. Note the occurrence of giant cells and numerous small cells which in the picture could be taken for the lymphocytic type of myeloma cell, but which under the microscope are seen to be the typical plasma cell type.

each nucleus a nucleolus is found. Within the nucleus, sparse chromatin in spokelike arrangement is spaced at the periphery. The nucleus is either globular, or more rarely, bean-shaped, and has a well defined nuclear membrane.

These cells, referred to most frequently as plasma cells, do not take the typical plasma cell stain by the Unna-Pappenheim or polychrome methylene blue technic; the perinuclear halo is almost always lacking, and the nucleus is slightly larger than the nucleus of the plasma cell.

A type of cell bordering on this description, found in nearly every case intermingled with the larger cells, is a smaller one from about 4 to 6 mu. It slightly resembles the lymphocyte in that the cell is poor in cytoplasm and the nucleus is relatively large in comparison with the rest of the cell; it is globoid and the chromatin, although sparse and of the same mural arrangement as the larger cells, appears more compact because confined in a relatively smaller space.

A frequent observation in the sections studied is the occurrence of apparent mitotic figures. The process is seen in many phases, and the frequency of its presence in the larger cells would seem to indicate that there is a relationship between this process and the multiple nuclei seen in larger cells.

Between these two types there are all stages of gradual transition and gradations, giving the impression that they are similar in derivation.

As for the so-called myeloblastic or myelocytic type of myeloma, we have repeatedly observed that concerning the same section, two authorities will differ between these two terms. Ewing, in cases 8 and 11 in our series, used the term myelocytic or myeloblastic, while Bloodgood used the term plasma cell type. In running through a series of twelve proved cases in rapid succession, one finds that these two cases do not stand out especially as atypical and fit in well with the so-called plasma cell type, although superficially, the nuclei do not appear to be as typically spokelike in arrangement. Many authors, in describing such cells in cases of multiple myeloma, are uncertain whether to class these cells in the plasma or myelocytic series (Berblinger, McCallum, Shennan, Schutz, Sexmuth, Klein, Stumm, Weber, Williams, Evans and Glynn), and some of these authors have thought that the apparent difference was due to fixing or staining methods.

In some cases, the differentiation was made on the basis of the oxidase reaction (Berblinger, Beck and McClearly, Vance, Warstat, Weinberg and Schwarz, Meiremet), and in other cases on the Unna-Pappenheim reaction for plasma cells (Aschoff, Hoffmann, Menne, McCallum and Neckarsumer). While the differentiation can thus be made in some cases, often it cannot be made by either oxidase reaction or by Unna-Pappenheim stain. Christian, in his study of six cases, believed that the myeloma cell is a transitional form not to be classed

as either plasma or myelocytic in type. Wallgren, in the study of thirteen cases, came to a similar conclusion.

As a rule, the myeloma tissue is rich in blood vessels. These are thin walled and lined with a single layer of endothelium (fig. 15). The blood vessels often have about them thin strands of fibrous tissue, although elsewhere in the tumor there is a noticeable lack of intracellular substance with a few fine fibrils here and there. There is often profuse hemorrhage into the tumor, and in almost all cases, there is a tendency for the tissue to be pervaded by red blood cells. Fat cells, giant cells and eosinophils are of common occurrence in myeloma tissue and, in most instances, are more numerous at the outskirts of the tumor, being the surviving cells of normal bone marrow.

The myeloma nodules are only apparently circumscribed, and microscopically, it is hard to tell where the tumor begins or ends. The growth appears to bring about a direct eating away of the bone, and the cells can be seen surrounding atrophying spicules of bones as if they were responsible for the disappearance of the osseous tissue (fig. 22). There appears to be a slight bone formation surrounding the tumor in earlier stages, which would account for the paper-thin bone shell often found. In other cases, the myeloma borders directly on the periosteum or infiltrates into adjacent tissue.

Only in rare instances do myeloma cells enter the circulation, in a manner so characteristic of the myeloblastic, myelocytic or lymphatic leukemias. These cells do not commonly pervade the hemopoietic tissue, such as the lymphocytes crowding into spleen and lymph glands in lymphosarcoma and lymphoid leukemia, despite the fact that in a small percentage of the cases, metastases are found in the liver and spleen. There is no change of the differential count in the sense in which one finds it in leukemia, nor is there the widespread crowding out of normal blood cell elements that one finds in the severe bone marrow diseases of aplastic anemia, and the blood does not lose its regenerative elements.

From this it would appear that the myeloma cell is not of the circulatory variety, but is peculiarly a marrow cell, restricted to some marrow function. Of the infectious or neoplastic nature of the disease of multiple myeloma, one can only say that the infectious or neoplastic nature of all tumors has neither been proved or disproved.

CLINICAL COURSE AND DIAGNOSIS

A brief turn in survey of the more characteristic features of multiple myeloma may serve to unify them into a more composite clinical picture and emphasize the typical course of the disease.

The onset is most often insidious, with indefinite wandering, rheumatic pains predominantly about the back and loins; or with progressive

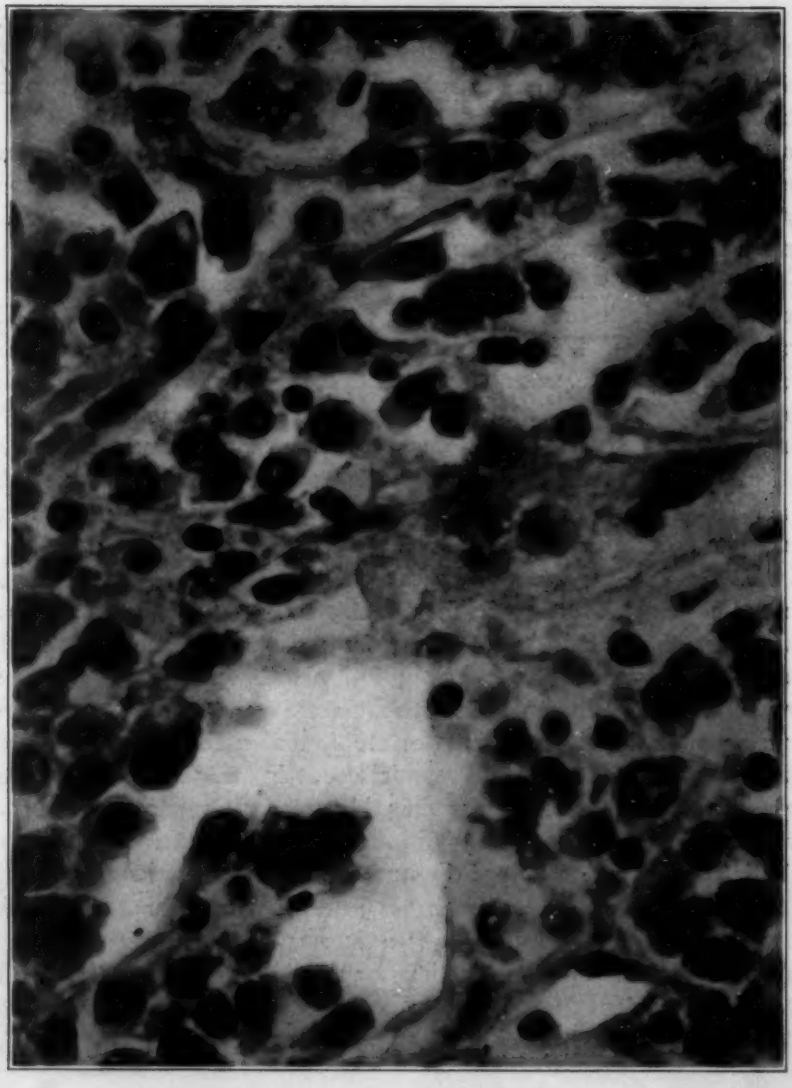

Fig. 21 (case 7).—Portion of a tumor rich in stroma. Typical chromatin arrangement of nuclei is again seen.

Fig. 22 (case 4).—Low power field showing the apparent erosion of bone by the invading tumor.

weakness in the form of general lassitude, sometimes marked by a loss of power in the legs adumbrating a gradual paraplegia. The patient's attention is first called to the malady by trauma, spontaneous fracture, the discovery of tumor or suddenly exacerbated pain brought on by some incident of muscular exertion. The complicating features of nephritis, gastric disturbances, or pulmonic changes may more rarely usher in the disease.

From this initial phase the patients pass on to a period marked by more continuous pains, by increasing deformities with kyphosis, tumor swellings, shrinking stature, multiple fractures and to paralysis with bedridden state. In some cases, the pulmonic symptoms become more acute and the nephritis more outspoken with anasarca and progressive cardiovascular changes.

Before this stage of advancing disease takes its fatal turn, a remission with temporary decrease or abatement in the intensity of the symptoms will frequently manifest itself, but in a short interval of time final failure sets in with cachexia and anemia. Flaccid paralysis ensues with decubitus, total incontinence and severe ascending urinary infection. Culminating in agonizing pains, the end comes on with terminal pneumonia, coma and death.

Not rarely, a patient may present an epitome of this entire range. In a case which we studied on the wards (case 1) there was, on admission, in addition to the marked skeletal deformity with shortening of stature, kyphosis, pathologic fracture and nodular tumors, a bronchitis and emphysema with asthmatic attacks, dilatation of the heart with systolic murmur, beginning paraplegia and strabismus; chronic nephritis with hypertension and hematuria, and increased metabolic rate and pronounced anemia. There had been an onset with an acute nephritis, and during the patient's stay in the hospital, there was marked remission of the disease. Later, when the patient returned home, there was an increasing paraplegia, recurring pain and an aggravation of all symptoms.

With such complexity in the clinical picture it is not surprising to find the initial diagnosis is often a mistaken one. Lumbago, spondylitis deformans, Pott's disease, nephritis, pleurisy, tabes dorsalis, Paget's disease, osteomalacia, osteitis fibrosa or visceral carcinoma with skeletal metastases are common errors in diagnosis. The symptomatology, otherwise misleading, is often clarified by beginning in the skeleton with both osseous and bone marrow destruction and tracing from these two fundamental changes in the skeleton on the one hand, and in the hemopoietic tissue on the other, the various disease manifestations of multiple myeloma.

The tumor formation in the ribs may lead to pathologic fracture or to subpleural nodules and these to hemothorax, pleurisy or even

empyema. Again, mere deformity of the ribs with accompanying pain and shallow respiration may lead to emphysema and bronchitis. The skeletal deformities in the spine are responsible for shortening of stature and compression of the spinal cord. This neural involvement in the form of radiculitis may give girdle pains and gastro-intestinal disturbance, or in the more ominous form of a paraplegia give incontinence and ascending urinary infection with pyelonephritis, the consequent bed-ridden state resulting in decubitus and hypostatic pneumonia.

On the other hand, the destruction of bone marrow with anemia is followed by lowered resistance and a tendency to secondary infection. A lowered platelet count makes these patients prone to hemorrhage and epistaxis. More theoretically, an achylia associated with the anemia may lead to gastritis. The excretion of Bence-Jones bodies apparently following on bone marrow disease goes hand in hand with a chronic nephritis which in turn makes for a terminal enterocolitis.

In this way, the disease picture in all its phases, as traced in table 2, can be shown to have its origin in skeletal tumors.

In lack of a characteristic onset, we must be on the lookout for presumptive evidence of the disease. Of the aggregate of signs and symptoms described, what are the outstanding characteristics which constitute such presumptive evidence?

1. Foremost in the series stands multiple involvement of the skeletal trunk in an adult. Spinal deformity should not be examined without including in that examination the ribs and the sternum. If this had been done in nearly every case in the series studied in which a diagnosis of spondylitis deformans or Pott's disease was made, the correct diagnosis of malignancy, at least, would probably have been hit upon, and in all likelihood myeloma itself diagnosed. Deformity of the spine, the parasternal rosary of tumor nodules, bulging and deformity of the ribs—these indicate multiple involvement of the trunk and are characteristic of the disease.

2. Occurring less frequently, but even more typically peculiar to this disease, is the pathologic fracture of a rib. Pathologic fracture of a rib in an adult is ample presumptive evidence for suspecting myeloma. In no other disease does it occur with a semblance of the frequency found in this condition.

3. The outstanding feature detracting from the diagnostic value of Bence-Jones bodies in myeloma is the failure to carry out this test as a routine in bone disease and tumor of the bone. This test is so simple, implying watching for an early precipitate when the usual test for albumin is carried out by slow heating, that it should not be omitted

TABLE 2.—*New Growth in the Bones; Tumor Formation Giving Rise to:*

I. Anemia			II. Bence-Jones Bodies Formation	III. Bone Destruction, Skeletal Deformities			
				Thorax		Spine	
Resistance lowered	Associated achylia	Lower platelets	Associated nephritis	Pathologic fracture	Barrel chest	Kyphosis	Shortening
Secondary infection (1)	Gastritis (2)	Hematemesis epistaxis (3)	Terminal enterocolitis (4)	Pleurisy empyema (1)	Bronchitis emphysema (2)	Paraplegia (3)	Cord compression Radiculitis (4)
				Decubitus and ascending genito-urinary infection	Bedridden hypostatic pneumonia	Girdle pains	Gastro-intestinal disturbances

as a routine in diseases of the skeleton. The albuminoid bodies are presumptive evidence for this disease. Their true diagnostic value, however, will not be known until this test is more applied in skeletal disease.

4. Although backache and radiating rheumatic pains are commonly found in myeloma, backache is sufficiently widespread clinically almost completely to nullify the diagnostic importance of this symptom. If in realization of the possibility of tuberculosis, metastatic carcinoma, sarcoma or myeloma of the spine, however, the clinician elicits a history of early compression of the cord (such as beginning loss of sexual potentia, difficulty in starting urination, or loss of power in the legs), this type of backache, exacerbated by movement, with radiating pains and associated signs of early paraplegia should be suggestive of multiple myeloma.

5. In some instances, an otherwise inexplicable and increasing anemia of the primary type will lead to roentgen-ray study of the bones when the facilities are available. Under these conditions, the possibility of multiple myeloma should be considered.

6. Finally, although adequate information is still lacking on this point, the presence of a chronic nephritis with nonprotein nitrogen retention and low blood pressure should arouse suspicion. In such cases, the urine should be tested for Bence-Jones bodies.

What in itself would not be evidence of conclusive diagnostic nature assumes through its corroborative association with similar evidence a diagnostic value of the first order. Thus, taken in pairs, triads or collectively as a group, the six conditions of (1) multiple involvement of the skeletal trunk in an adult, (2) pathologic fracture of a rib, (3) the excretion of Bence-Jones bodies, (4) characteristic backache with signs of early paraplegia, (5) an otherwise inexplicable anemia and (6) chronic nephritis with nitrogen retention and low blood pressure are of cardinal diagnostic importance for multiple myeloma.

The majority of cases of myeloma fit into a syndrome, embracing several of these salient features of the course of the disease which has been described.

PROGNOSIS AND TREATMENT

The prognosis is uniformly unfavorable, the average duration of the disease being about two years after the date of recognition. The longest duration of any proved case is five and one-half years (Wallgren, our case 1). The duration of the disease appears to be uninfluenced by treatment, although roentgen-ray therapy has been reported as bringing about remissions; however, as we have pointed out, remissions occur spontaneously. With no proved case reported as cured it is evident that palliative symptomatic treatment only is available. Nursing care

to avoid unnecessary pain on motion and pathologic fractures is important. When fractures occur, the ordinary methods of treatment by fixation may be given, as pain is thus minimized and healing often accomplished. Morphine for pain, liver diet and tonics for anemia and inhalations for respiratory complications are helpful.

SUMMARY

The history of multiple myeloma has been briefly sketched and the cases published since 1848 compiled. Males were found affected in 70 per cent of the cases, the age group from 40 to 70 predominated, and the geographic distribution found to extend to all parts of Europe, to North and South America and to Australia with members of the black

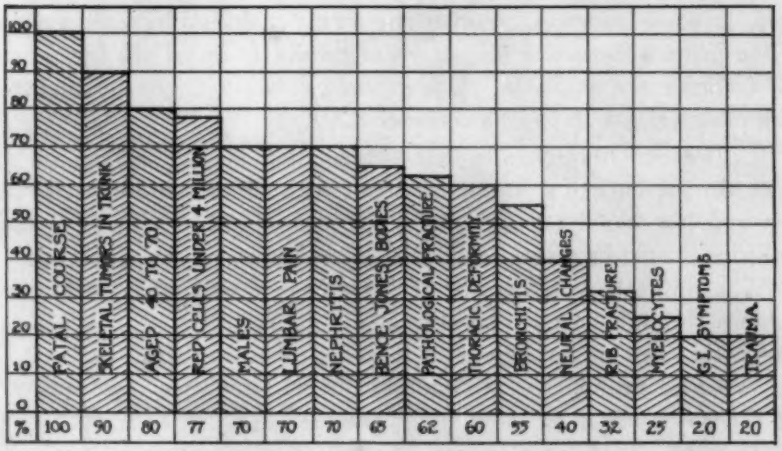

Fig. 23.—Incidence by percentage of leading symptoms of myeloma.

and yellow races included. Myeloma was found to constitute about 0.03 per cent of malignancy of all types, with the etiologic factors of heredity, trauma and infection playing little, if any, rôle in its production.

Among the clinical symptoms, intermittent rheumatic pains were found a leading symptom of onset, localized chiefly in the lumbar region with radiations to the legs and girdlelike sensations about the lower part of the thorax, aggravated by motion and typified in their course by insidious onset, sharp exacerbation, remissions and final agonizing termination.

Multiplicity of tumor involving the thoracic cage was present in over 90 per cent of the cases, the tumors being relatively small and elastic, with occasional pulsation, crepitation and regression. Skeletal deformity was shown to occur in 60 per cent of the patients characterized by a sunken sternum, "parasternal rosary," dorsal kyphosis, shortening of stature,

and pathologic fracture with an incidence of 63 per cent, affecting the ribs most frequently.

Bronchitis and emphysema associated with thoracic demormities was found in 55 per cent of the series, followed by a terminal pneumonia in a majority of these instances.

Neurologic involvement secondary to bony change was noted in 40 per cent of all cases, with radiculitis and paraplegia of the extremities predominant features.

Bronchitis and emphysema associated with thoracic deformities was emphasized as a feature in two thirds of the patients with myeloma, and the almost constant association of Bence-Jones bodies in the urine with this condition was pointed out.

Among the less common manifestations of the disease were noted gastro-intestinal disturbance and metastatic involvement of the lymph glands, liver and spleen.

Bence-Jones bodies were found to be excreted in 65 per cent of the cases and the simple laboratory tests for their demonstration recapitulated. The occurrence of these bodies in the urine of patients suffering from other bone diseases and diseases of the hemopoietic tissues was pointed out and a list of the cases given.

The degree and nature of the anemia, characteristic of myeloma, was described and the various pathologic changes in the white blood cells enumerated.

The peculiarity of the roentgen-ray observations in this disease with multiple punched out areas of bone destruction occurring primarily in the trunk and less frequently in the skull and proximal ends of the extremities was indicated. The possibility of rare metastases to the lung and subpleural nodules simulating pulmonic involvement was also mentioned.

The uniformity of the microscopic picture in myeloma was emphasized and evidence cited that there is probably but a single type of marrow cell occurring in various stages of development in all cases.

Lastly, a composite clinical picture of the disease entity of multiple myeloma was sketched with the original tumors of the bone marrow shown responsible by bone destruction on the one hand, and marrow changes on the other, for all the various clinical and pathologic changes described.

Six cardinal features of myeloma were pointed out: (1) multiple involvement by tumor of the skeletal trunk, (2) pathologic fracture of a rib, (3) Bence-Jones bodies in the urine, (4) characteristic backache with signs of early paraplegia, (5) an otherwise inexplicable anemia and (6) chronic nephritis, nonprotein nitrogen retention and low blood pressure.

REPORT OF CASES

CASE 1.[5]—J. W. E., aged 40, white, a farmer, was admitted to the Johns Hopkins Hospital on Oct. 21, 1926, complaining of "kidney trouble." There was a family history of cancer in one uncle. He had suffered the usual ailments of childhood, having had typhoid at the age of 8. With the exception of frequent colds and asthma for the past three years, his health had been good. Ten years before admission to the hospital, while he was lifting a heavy weight, a severe backache had started which had lasted several days. Three years later, this recurred under similar circumstances. Two years later, for the first time, an acute spontaneous pain occurred in the back. Two years before admission, an operation had been performed for hemorrhoids; this was followed three weeks later by an attack of acute nephritis with hematuria, headache, palpitation and anasarca. After the acute symptoms subsided, nocturia and pounding headaches persisted. In March, 1925, on inadequate provocation, he fractured a rib. Following this, there were dull aching pains between the shoulders radiating down his back and around his ribs. From March to May, 1925, the patient remained in bed, with severe pains in the bones and muscular twitchings which made him feel as though he were being "drawn together." Roentgenograms taken at the time showed "cancer of the bones." During the past year he has noticed decrease in his stature and bending of his back. He lost 20 pounds (9 kg.) in weight.

On physical examination, the patient presented a striking picture. He was emaciated, pale and weak, with sallow complexion and labored respirations. The arms and legs were of normal length. He stood with feet wide apart; his normal lumbar lordosis had disappeared, and an upper dorsal kyphosis was present which allowed his chest to sink almost to the pelvis. Small bony nodules were found over his right humerus, the inner end of the left clavicle and the right third rib. The left eleventh rib was tender and easily misplaced. The chest was filled with coarse râles, the respirations were wheezing, the heart was enlarged and the arteries were thickened. The pulse rate was 90, the blood pressure 175 systolic and 100 diastolic. The liver and spleen were palpable. The patient weighed 125 pounds (56.7 Kg.). The sputum was negative for tubercle bacilli. The blood count revealed: hemoglobin, between 35 per cent and 40 per cent (Sahli); the red count, between 1,600,000 and 1,900,000, and the white cell count, between 8,000 and 12,000 on five different examinations over a period of two weeks. The differential count was normal with 70 per cent neutrophilic polymorphonuclears. The nonprotein nitrogen in the blood was 34 mg. per hundred cubic centimeters; the uric acid, 31.1 mg. per hundred cubic centimeters; phosphates, 4.8 mg. per hundred cubic centimeters; calcium, 10.8 mg. per hundred cubic centimeters, and chlorides, 649 mg. per hundred cubic centimeters. The Wassermann test of the blood was repeatedly anticomplementary. The excretion of phthalein was 55 per cent for two hours; the urine showed staphylococci and hemolytic streptococci. The Bence-Jones test was postive on four different occasions (although often negative). Urinalysis also showed 3.2 Gm. of serum albumin per liter, with red and white cells and granular casts present on microscopic examination. The excretion of chloride in the urine on salt free diet was 5.5 Gm. The vital capacity was reduced to 1.8 to 2.5 liters; the basal metabolic rate was plus 26.

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5. This case is also referred to by Longcope: International Clinics **2**:91, 1927. Perlzweig, Debrue and Geschickter: Hyperproteinemia and Multiple Myeloma, J. A. M. A. **90**:755 (March 10) 1928.

Special blood chemistry studies by Dr. Perlzweig[6] revealed: a refractive index of 1.3610 (normal 1.3450 to 1.3500); total protein, 12.32 (normal 6.5 to 7.5); albumin, 0.23 (normal 4.0 to 5.5); globulin, 10.11 (normal 2.0 to 2.5); fibrin, 0.79 (normal 0.20 to 0.30), and an albumin to globulin ratio of 12/88 or 0.13 with the normal 75/25 to 55/45 or 3.0 to 1.22.

Roentgen-ray studies showed multiple involvement of the skull, ribs, spine, clavicles and the long bones of the upper extremities by rarefied and small punched out areas with fracture of the eleventh left rib.

The left femur was examined surgically and showed a friable, highly cellular mass beneath the cortex. A portion removed on microscopic examination showed multiple myeloma of the plasma cell type (fig. 19).

The course in the hospital showed symptomatic improvement with disappearance of the respiratory difficulty and a fall in the blood pressure from 170 systolic and 102 diastolic to 125 systolic and 90 diastolic. The albumin in the urine decreased but did not disappear. The patient was discharged with the underlying disease process unaltered.

Microscopic examination of the bone marrow showed little stroma; solid masses of tumor cells both of plasma cell and small lymphoid cell varieties; many bone marrow eosinophils and cells of the early myelocytic series; many giant cells of the epulis type with the plasma cell type predominating.

Case 2.—C. D., a man, white, aged 51, was admitted to the Johns Hopkins Hospital on Jan. 21, 1925, with a complaint of pain across the back and the right side. The family history was noncontributory. He had had the usual diseases of childhood including scarlet fever. The past history also showed typhoid fever, gonorrhea and alcoholism. The patient had suffered with constipation and had had hemorrhoids fifteen years before admission to the hospital. There was nocturia and complaint of gastric disturbances. He was 66 pounds (29.9 Kg.) under his best weight.

The onset of the present illness was eighteen months before admission and occurred with rheumatic pains in the right shoulder following on a gradual loss of weight extending over a period of four years. Two and one-half months before admission, he developed a sharp pain in the right side while pitching horseshoes. Rapid loss of weight and strength followed with anorexia and swelling of the right clavicle and marked weakness of the legs.

On physical examination, there was emaciation and weakness with a definite icteric tinge to the sclerae. Swelling was present over the middle of the right shoulder, over the ninth and tenth ribs posteriorly and over the clavicle on the right side. The heart and lungs did not show abnormalities; the peripheral vessels were thickened and the blood pressure was 110 systolic and 85 diastolic. The abdomen was protuberant; the liver was palpable. There was marked weakness of the lower extremities with hyperactive knee and ankle jerks. The Oppenheim and Babinski reflexes were positive on both sides. The prostate was enlarged. The clinical impression was carcinoma of the prostate with skeletal metastases.

The blood showed: hemoglobin, 55 per cent (Sahli); red blood cells, 3,224,000; white blood cells, 6,080 with the differential count showing 2 per cent myelocytes. The Wassermann reaction was negative. The urine, which was essentially normal on admission, showed albumin, red and white blood cells and casts when a retention catheter had been used following the development of a paraplegia. Examination for Bence-Jones bodies was repeatedly negative.

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6. Perlzweig (footnote 5, second reference).

Roentgen-ray examination showed multiple destructive lesions of the bones in the thorax, pelvis and skull with pathologic fracture of the eighth and ninth ribs and the clavicle on the right side.

The patient failed rapidly. Complete paraplegia developed with ascending urinary infection and anuria on the last two days. The temperature did not rise above 100 F.

At necropsy, the anatomic diagnosis was multiple myeloma involving the right clavicle and acromion, the seventh, eighth, ninth and tenth ribs on the right with pathologic fracture of the ninth rib and erosion of the seventh, eighth and ninth vertebrae, with softening of the cord at this level. The tumor masses were soft and variegated white and red. There was a fibrinous pleurisy on the right side. The liver was enlarged with fatty degeneration. There was cloudy swelling of both kidneys with bilateral pyelonephrosis and pyelitis. Cystitis and a mucous colitis were present. On microscopic examination the tumor was diagnosed plasma cell type multiple myeloma.

Microscopic examination of bone marrow showed evidence of meager stroma, rather compact homogeneous masses of plasmalike cells. Red blood cells were sparse. An occasional cell of the polymorphonuclear series was seen.

Case 3.—Mrs. E. W., white, aged 71, was referred to Dr. Bloodgood on June 20, 1926. She was seen in consultation with the complaint of tumor in the left axilla. There had been malignancy in both the mother's and father's family. The patient had had malaria at the age of 16. She was the mother of six children and had had two miscarriages. She had had hemorrhoids at the age of 61. The present illness dated back two years, at which time the patient had been operated on for a tumor in the left axilla. This tumor had been present for fifteen years, but four months before examination had begun to enlarge and cause pain. At the time of excision of the tumor, the diagnosis was old healed tuberculous glands. The incision broke down and in March, 1926, the patient complained of pain in the left shoulder with limitation of motion in the joint. The glands had not recurred. The pain continued; the patient lost weight and there was bronzing of the skin.

On physical examination, a mass was found in the right epigastrium which was painless. There was a pathologic fracture of the left humerus with evident tumor formation. Examination of the heart, lungs and pelvis was negative. The urine showed 3 plus albumin with many bacteria, but was negative for Bence-Jones protein. The blood showed red cells, 2,490,000; hemoglobin, 50 per cent (Sahli); white cell count, 5,800, with a differential count of neutrophilic polymorphonuclears, 53 per cent, lymphocytes, 37 per cent, large monocytes and transitional cells, 10 per cent. The Wassermann test of the blood was negative. The blood pressure was 140 systolic and 90 diastolic. The pulse rate was 86; the temperature, normal.

The roentgen-ray examination showed mottled areas in the left scapula, humerus, ribs and femur. A pathologic fracture was noted through the neck of the humerus.

Following a biopsy, the patient became progressively worse and died in coma.

At autopsy, soft tumor masses were found in the shaft of the humerus, in the head and neck of the scapula on the left. The ribs and sternum were involved by tumor and easily broken. The lungs and mediastinal glands were free from tumor. The liver showed fatty degeneration. The kidneys showed chronic interstitial nephritis. There were gallstones with a fibrotic gallbladder.

On microscopic examination, the tumor was diagnosed multiple myeloma of the plasma cell type. The tumor tissue was particularly homogeneous in type with an occasional large myeloma cell among the masses of the more typical plasma cell type. On the outskirts of the tumor, there was much hemorrhage. Stroma was found only about the blood vessels.

CASE 4.—C. F. T., aged 66, a man, white, was admitted to the Johns Hopkins Hospital on Sept. 9, 1922, with a complaint of weakness. The family history was unessential. He had had typhoid fever in boyhood with some polyuria and nocturia in the past few years. The present illness began ten months previous to admission with bulletlike pains of short duration in the left side following an attack of influenza. The patient began to feel weak about the waist and was confined to bed. Loss of weight was rapid (70 pounds [31.8 Kg.] in nine months). Recently, there had been epigastric discomfort.

On physical examination, there was evident loss of weight, marked weakness and some dyspnea. The trachea was deflected to the right; the lungs did not show descent at the bases and the percussion note was emphysematous. The peripheral blood vessels were leathery; the blood pressure was 104 systolic and 62 diastolic.

The liver was enlarged and its edge palpable. The spine was rigid in the lumbar region with thoracic lordosis and lumbar scoliosis. There was tenderness over the third and fourth lumbar vertebrae. The blood showed a hemoglobin of 40 per cent (Sahli) with 2,168,000 red cells; a white cell count of 11,800 and a normal differential count. The Wassermann reaction was negative. The urine showed 1 plus albumin and a positive reaction for Bence-Jones proteins. Cystoscopic examination revealed pyelitis on the left side. Phthalein excretion was 50 per cent for two hours.

The roentgen-ray examination showed multiple tumor involvement of the spine, chest and pelvis. The clavicle and first rib on the right were expanded with tumor, and the femora were involved at their upper ends.

Following the cystoscopic examination the patient became febrile and confused. He died with a terminal bronchial pneumonia. The temperature was 105 F.

At autopsy, the anatomic diagnosis was multiple lymphoid myeloma involving the vertebra, sternum, ribs and femora; terminal bronchial pneumonia; acute splenic tumor, chronic nephritis, with fresh multiple hemorrhages along the entire genito-urinary tract; multiple abscesses of the kidney with healing perirenal abscess, serofibrinous pleurisy, strawberry gallbladder and internal hemorrhoids.

Microscopic examination of the tumor showed finely reticulated stroma between eroded masses of bone spicules filled with plasmalike cells intermingled with large cells of the same variety. Many small blood vessels were seen permeating the reticulated cellular masses. Occasional giant cells of the epulis type were seen, together with masses of the small variety of cells.

CASE 5.—A. G., a man, white, aged 71, was referred to Dr. Bloodgood on April 27, 1922, with a complaint of sciatic rheumatism. The family history was noncontributory. The past history revealed failing health for the past twenty years, with bilateral "rheumatism" of the lower extremities for the past fifteen years. The present illness began with a pathologic fracture one year before examination which involved the upper third of the right femur. The patient was treated for six months; poor results were obtained.

On physical examination, there was marked loss of weight and weakness. There was a pigmented nodule over the left clavicle and a raised area at the

junction of the sternum and third left rib. Ulcerated areas were found over the right thigh and a fracture of the upper third of the right femur. The result of the examination of the heart and lungs was negative.

The examination of the blood showed a hemoglobin of 40 per cent; red cells, 3,352,000; white cells, 12,200; a differential count was not recorded. The urine was negative for Bence-Jones proteins.

The roentgenogram showed destruction at both ankles, left shoulder joint, left third rib and right upper femur with a healed fracture of the femur. The Wassermann test of the blood was negative.

At necropsy, the anatomic diagnosis was myeloma involving the femur with pathologic fracture of the left clavicle, sternum and left third rib. There was an old obliterating pleurisy.

Microscopic examination of the tumor mass showed more than the usual amount of stroma and a variation of the myeloma cell toward the myelocytic type, but with the plasma cell type much in evidence.

Case 6.—M. C., a colored woman, aged 37, was referred to Dr. Bloodgood on Dec. 21, 1921, with a complaint of pain in the back and left side. The patient's mother had died of pulmonary tuberculosis. The past history revealed the usual diseases of childhood with malaria in youth. She had been pregnant ten times and recently had had some leukorrhea.

The present illness began one year before examination with pain in the back and the left side. Three months before examination the pain was severe enough to force the patient to bed. She continued to be bedridden. A pathologic fracture and a marked loss of weight occurred during this period.

On physical examination, the patient showed marked loss of weight and tenderness over the lumbar region. There was a pathologic fracture of the neck of the right femur. The results of examination of the heart and lungs were negative. The spine did not show any abnormalities. The blood pressure was 130 systolic and 80 diastolic. The blood showed a hemoglobin content of 77 per cent; red cells, 4,250,000; white cells, 13,200 with a differential of 72 per cent polymorphic neutrophils; 13 per cent lymphocytes, with 15 per cent large mononuclears and transitionals. The urine showed a trace of albumin with white blood cells, red blood cells and casts. Bence-Jones bodies were found. A cystoscopic examination showed pyelonephritis; the phthalein appeared in seven minutes.

The roentgenogram showed bone destruction in the pelvis and right femur. Complete studies were not made.

The course was steadily downward, with marked loss of weight, fever and terminal pneumonia. The patient died on April 6, 1922.

At necropsy, visceral involvement was not found. There was a subpleural nodule on the posterior surface of the right lung. The anatomic and microscopic diagnosis was multiple myeloma of the plasma cell type.

Microscopic examination of the tumor mass revealed a typical but highly fibrous type of myeloma with great variation of the cell sizes.

Case 7.—W. H. H., a man, white, aged 55, was admitted to the Johns Hopkins Hospital on Sept. 3, 1921, with a complaint of pain in the lumbar region and legs. The family history was noncontributory. He had had the usual diseases of childhood, and typhoid at the age of 41, influenza at 53 and pneumonia at 55. He had suffered many years from nasal catarrh and headaches. There were many pigmented moles. The present illness began one month prior to admission with pain in the lumbar region following a second attack of influenza. Pain in the lumbar region persisted and radiated to the legs.

Physical examination revealed a well nourished white, middle-aged man, with neglected teeth and mucous membranes of a fair color. The lungs were normal. The heart was not enlarged; a soft systolic bruit was present at the apex. The blood pressure was 135 systolic and 80 diastolic. The abdomen was normal; the liver and spleen not enlarged. The lumbar spine was held rigidly with muscle spasm over the seventh thoracic vertebra, more prominent on the right. In the anterior axillary line over the seventh right rib was a fusiform swelling which, on exploratory incision, showed a pathologic fracture of the rib.

Examination of the blood showed: red cells, 2,092,000; hemoglobin, 55 per cent; white cells, 5,500; the differential count showed 10 per cent large mononuclears and transitional cells. The Wassermann test of the blood was negative. The urine gave a two plus reaction to the albumin test with white blood cells and casts. The excretion of phthalein was 40 per cent for two hours. The presence of Bence-Jones proteins was doubtful on the basis of the limited tests performed.

Roentgen-ray examinations showed multiple involvment by destructive tumors of the bone of the thorax with compression of the seventh and eighth dorsal vertebrae and fracture of the seventh right rib. The skull was rarefied and the frontal sinuses were large.

The patient had a fever of from 100 to 103 F. and toward the end became confused, agitated and had moderate delirium; finally he became comatose, dying on June 21, 1922.

At necropsy, the anatomic diagnosis was myeloblastic myeloma involving the seventh and eighth dorsal vertebrae, the eighth rib on the right with pathologic fracture; arteriosclerosis; chronic diffuse nephritis with calcification and lipoma of the renal cortex, and terminal bronchopneumonia.

Microscopic examination showed different types of cells dominating in different portions of the tumor; around vessels and bone spicules a homogeneous type of myelocytic cell was seen, while in the fatty matrix of the marrow the plasma cell type was interspersed, with eosinophils predominating. At points in the tumor there was intermingling of all types of cells.

Case 8.—Mrs. S., a white woman, aged 72, was referred to Dr. Bloodgood on May 21, 1922, with a complaint of rheumatic pains in the arm of two years' duration. While carrying a bundle, something "gave way" in the left forearm. Localized pain or swelling at the site of the pathologic fracture had not been noted previous to the accident.

On physical examination, a yielding tumor was found about 25 cm. in diameter and 22 cm. below the left elbow. Small palpable nodules and depressions were present in all the long bones, and a large depression was palpated in the occiput of the skull. The remainder of the physical examination did not disclose anything of special interest.

The examination of the blood showed a hemoglobin content of 74 per cent with 4,668,000 red cells, 8,800 white cells, and a differential count of 53 per cent polymorphonuclear neutrophils and 39 per cent lymphocytes; the remaining 6 per cent was comprised of large mononuclears and transitionals. The Wassermann test of the blood was negative. The urine showed a 1 plus albumin and a positive test for Bence-Jones proteins.

Roentgen-ray examination showed fifty-six punched-out circular areas of various sizes scattered through the spine, sacrum, skull and the long pipe bones.

The left arm was amputated, but death followed shortly afterward.

Pathologic examination of the amputated arm showed a large soft, purple tumor, involving the left ulna with complete bone destruction in the area of the tumor.

Microscopic examination showed sparse reticulation, many thin walled blood vessels, and densely packed cells. The size of the cells varied from small cells with little cytoplasm to large multinuclear cells with a large amount of cytoplasm. The nuclei were typical, with mural arrangement of a sparse amount of chromatin and a central nucleolus.

CASE 9.[7]—C. M., a colored woman, aged 50, for ten years had had rheumatism and a cough in winter. One year before examination, she had had pain in the right hip and knee, followed by fracture of the right arm eight months later. Recently, there had been swelling on the head and fracture of the right leg.

Physical examination showed pallor and emaciation, false motion with pain of the right arm and leg, and tumor masses of the clavicles, the skull, the left scapula, and of the extremities and at the costochondral junctions.

The blood showed a hemoglobin content of 52 per cent; red cells, 3,548,000; white cells, 4,500 with a differential count essentially normal. The urine gave a 4 plus reaction to the albumin test with casts and Bence-Jones protein definitely present.

The patient failed rapidly, and at necropsy the anatomic diagnosis was multiple myeloma involving the femur, ileum, clavicle, sternum, skull and scapula with chronic nephritis, arteriosclerosis, and myomati uteri and healed tuberculosis of the lungs.

Microscopic examination showed sparse stroma and many blood vessels with walls lined by single endothelial cells (fig. 5). The cells were three general sizes—a small dense cell, with the nuclear mass appearing solid, but which on further examination had the same arrangement as the larger cells; a cell of medium size of the plasma cell type, and a larger, occasional giant cell with several nuclei.

CASE 10.—B, a man, white, aged 44, was referred to Dr. Bloodgood on Dec. 19, 1924, with a complaint of swelling and pain in the left knee. The family history was negative. In the past he had always had general good health. There was no history of gastric or urinary disturbances. The present illness began three years before examination with pain and swelling in the left knee. The pain was continuous, but the swelling intermittent. Six months previous to admission, the pain had disappeared. The swelling became permanent. The leg was useless and the patient began to use crutches. Two months before admission, there had been an onset of fatigue and weakness. There was history of trauma to the knee five years before. On physical examination, the patient showed evident loss of weight. The mucous membranes were of good color. The heart and lungs were normal. The left leg had been amputated through the middle of the thigh.

The results of analyses of the urine were negative and did not show Bence-Jones bodies. The blood showed a hemoglobin of 70 per cent; red blood cells, 4,480,000; white blood cells, 6,000; a differential count showed 70 per cent polymorphoneutrophils, 4 per cent eosinophils, 2 per cent basophils and 24 per cent lymphocytes. Excretion of phthalein was normal.

Roentgen-ray examination showed a central tumor in the shaft of the femur with bone destruction and perforation of the bone shell and mottling of the marrow cavity.

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7. This case, no. 9, on file in the surgical pathological laboratory of the Johns Hopkins Hospital has been reported elsewhere by Hamburger and by McCallum. A summary only is included here for completeness.

The gross specimen of the amputated leg showed a large soft, but not hemorrhagic, tumor in the lower third of the femur erupting through the bone and involving soft tissues.

Microscopic examination showed large pale cells with typical nuclei, ranging up to giant multinuclear cells. The chromatin, however, was much more sparse, yet murally arranged. Mitotic figures were seen.

CASE 11[8]—C., a man, white, aged 37, with a previously negative history, had an illness which began fourteen months after an injury to the right shoulder. At first there was pain and tenderness over the right clavicle followed by a symmetrical tumor three weeks later. The tumor recurred in the first rib two months after resection of the clavicle. The patient became progressively worse, and death occurred four months after recurrence of the condition. Diplopia developed shortly before death.

Bence-Jones bodies were constantly present in the urine; there was no evidence of nephritis. The tumor was diagnosed myelocytic myeloma on microscopic examination by Welch, Bloodgood, McCallum and Crile.

CASE 12.—J. S., a man, white, aged 62, was admitted to the Johns Hopkins Hospital on Nov. 16, 1922, with a complaint of pain in the back. The family history was negative. He had had nocturia in the past, and recently, epistaxis with pathologic fracture of the wrist. The present illness began two years before admission to the hospital, with pain in the shoulders and back radiating to the ribs. He was treated at the Johns Hopkins Hospital Dispensary for hypertrophic arthritis. One year previous to admission, a nodule appeared on the sternum in the jugular notch. On physical examination, evident loss of weight and pallor of the mucous membranes were found. There were dorsal kyphosis and rigidity of the whole spine with pain on flexion. There was a palpable tumor in the episternal notch to the right side and top of the sternum. The heart and lungs were normal. The blood pressure was 158 systolic and 108 diastolic. The liver and spleen were not palpable.

The blood showed a hemoglobin content of 35 per cent; red blood cells, 2,000,000; white blood cells, 6,800; a differential count showed 48 per cent polymorphonuclears, 40 per cent lymphocytes, 11 per cent mononuclears and transitionals. The Wassermann test was negative. The urine showed Bence-Jones proteins—21.7 Gm. in twenty-four hour specimen of 1,800 cc. The excretion of phthalein for two hours was 30 per cent. Urine from the case preserved in the clinical laboratory shows the Bence-Jones reaction still present eight years later.

The roentgenogram showed slight but multiple involvement of the vertebral columns. The patient did not remain in the hospital. Biopsy was not obtained.

CASE 13.—W. T. S., a man, white, aged 59, was admitted to the Johns Hopkins Hospital with the complaint of kidney trouble and general weakness. The family history was noncontributory. He had had malaria ten months before admission. There was a history of epistaxis and hemorrhoids.

The present illness began fifteen months before entry, with cachexia, irritability and urinary difficulty. There was increase in nocturia and difficulty in controlling the flow, and pain in the precordium.

On physical examination, there was loss of weight and pallor of the mucous membranes. The clavicles were prominent and right dorsal scoliosis existed.

8. This case, no. 11, on file in the surgical pathological laboratory of the Johns Hopkins Hospital has been mentioned by Bloodgood: Progressive Medicine, 1906, vol. 4, p. 229. This summary only is included here for completeness.

There were tumor masses over the tenth, eleventh and twelfth dorsal spines. There was an elevation over the parietal bone and tenderness over the fourth rib on the right. The lungs were normal. The heart was slightly enlarged to the left and a soft systolic murmur was heard at the apex. The liver and spleen were not palpable. The rectal sphincters were relaxed. The blood picture showed: hemoglobin, 50 per cent; red blood cells, 2,432,000; white blood cells, 10,760; the differential count showed 66 per cent polymorphonuclears, 28 per cent lymphocytes, 6 per cent mononuclears and transitionals. The Wassermann test of the blood was negative. The examination of the urine showed 3 plus albumin and the test for Bence-Jones bodies was positive. Microscopically, the urine showed red blood cells, white blood cells and casts. The excretion of phthalein showed a total of 9 per cent for two hours on one occasion and 18 per cent on another. The Mosenthal test showed fixation of specific gravity. Gastric analysis did not show any free hydrochloric acid, but showed a combined acidity of 6 degrees. The guaiac test for occult blood was negative. The percentage of acidity was 0.02. The blood chemistry studies showed nonprotein nitrogen from 70 to 80 mg. per hundred cubic centimeters with a carbon dioxide combining power of from 18 to 27 volumes. Chlorides were from 585 to 593 mg. per hundred cubic centimeters; creatinine, 3.3 mg. and 3.8 mg. per hundred cubic centimeters and sugar 0.083 mg. per hundred cubic centimeters.

The roentgen-ray examination showed multiple involvement of the skull, humerus and femora. The basal metabolic rate was minus 4.

The patient did not remain in the hospital. Biopsy was not obtained.

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PERFORATION OF THE DIAPHRAGM

THE RESULT OF INTRA-ABDOMINAL SUPPURATION: REPORT OF UNUSUAL CASES *

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Ordinarily the diaphragm is considered an efficient barrier between the abdominal and pleural cavities, even in cases of suppuration. While infection may spread in either direction by way of the lymphatics, extension by loss in continuity of the diaphragm is rather unusual and is particularly uncommon in cases of acute generalized suppurative peritonitis. The following cases briefly illustrate three different types of intra-abdominal inflammation responsible for intrapleural suppurative conditions.

REPORT OF CASES

CASE 1.—R. G., aged 44, had had a hysterectomy and a right salpingo-oophorectomy performed for a tubo-ovarian abscess which involved the tip of the appendix. Twenty-one days later, after a febrile course, a right perinephritic abscess was opened and drained. Intermittent pain persisted in the right side. Dulness developed at the base of the right lung, accompanied by an irritating, nonproductive cough. Later, a moderate amount of foul-smelling, purulent material was expectorated. The patient died on the thirty-sixth day following the first operation and fifteen days after the perinephritic abscess was drained.

The important points at autopsy were as follows: The perirenal tissue surrounding the right kidney was deeply congested and showed a small amount of seropurulent material. Between the upper pole of the kidney and the liver was a small quantity of pus. This extended over the surface of the liver, just anterior to the right lateral ligament. Passing upward, it perforated the right coronary ligament and formed a second abscess in the space between the diaphragm, the extraperitoneal portion of the liver and the folds of the coronary ligaments. This abscess contained about 60 cc. of thick yellowish-white pus.

The base of the right lung adhered to the dome of the diaphragm by a fresh plastic exudate, 1 mm. in thickness, that was easily separated. On separation, the dome of the diaphragm "bulged" upward and showed a small perforation about 2 mm. in diameter at its highest point, from which a thick yellowish pus exuded. Immedately overlying this diaphragmatic perforation was a corresponding opening in the base of the right lung, from which a similar material also exuded on pressure. This perforation in the lung was surrounded by a consolidated area of irregular shape, roughly 5 by 7 cm. On section, it was found to contain a small abscess cavity about 1 cm. in diameter, just beneath the pleura.

CASE 2.—S. J. H., aged 40, about four weeks before admission to the hospital, complained of pain in the epigastric region, unassociated with nausea, vomiting, rise in temperature or pulse rate. The following day the pain became more or less localized in the right hypochondriac and iliac regions, but abdominal rigidity

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* From the Laboratory of the Samaritan Hospital.

or tenderness could not be elicited and there was no increase in temperature or pulse rate. The pain gradually subsided, only to recur again in a few days. These attacks of ill defined and poorly localized pain persisted for about three weeks, when the patient began to expectorate large quantities of pus, which relieved him from pain. At the same time, his temperature and pulse rate increased. Finally, the day before his death, the patient was rushed from the country to the hospital in an effort to save his life. An operation was not attempted because of the poor condition of the patient. He died a few hours after admission.

The pertinent conditions found at autopsy were as follows: The abdomen was markedly distended and tympanitic. Free fluid or pus were not found in the peritoneal cavity. Both large and small intestines were greatly distended. On separating the cecum from the muscles of the flank an abscess was opened; it contained but a small quantity of pus (about 5 cc.). The abscess cavity was lined with a shaggy, dirty, greenish-black, scant exudate. Adherent to the posterior part of the cecum, in the wall of the abscess, lay the appendix, which was in a necrotic condition. The abscess cavity continued upward, between the posterior part of the ascending colon and the posterior abdominal wall, as a sinus tract about 1 cm. in width and of a greenish-black, moist appearance, containing necrotic material with a stale fecal odor. The portion of the colon that formed the anterior wall of this tract was black and necrotic and tore on the slightest manipulation. The tract continued upward, lateral to the perirenal tissue and behind the right lobe of the liver. It communicated with the right pleural cavity through a perforation in the dome of the diaphragm in its extraperitoneal portion, between the coronary ligaments of the liver. The tract throughout its entire length presented the same blackish appearance. There was no collection of pus immediately below the diaphragm.

The right pleural cavity showed a hemorrhagic, purulent exudate over the base of the lung, which was adherent to the diaphragm. The lung was nodular and irregular, due to the areas of consolidation, which were dark red, irregular and slightly raised above the surface. On section, they showed a softened, yellowish center, surrounded by a firm, reddish zone of varying width. Many such nodules were scattered throughout the lobes of both lungs.

CASE 3.—Z. H., aged 23, one week before admission, had had a criminal abortion performed by insertion of a rubber catheter. This was passed the next day and was followed, two days later, by a fetus and placenta. On the day of admission to the hospital, the patient developed severe epigastric and lower abdominal pain, unaccompanied by vaginal bleeding or discharge. On admission, the temperature was 102 F.; the pulse rate, 120 and respirations, 25. The abdomen was rigid and tender throughout. There was a suggestion of a friction rub at the left base. The blood count revealed 27,600 white blood cells and 90 per cent polymorphonuclears. Two days after admission, nausea and vomiting developed, which became fecal two days later. The temperature was septic. The patient did not complain of difficulty in breathing or of pain in the chest. Death occurred on the seventh day.

The salient points at autopsy were as follows: Gas escaped as soon as the peritoneum was opened. The enormously distended intestines were matted together and contained pockets of thick, yellowish, foul-smelling pus between the coils. A perforation could not be found. There was a thick mass of somewhat inspissated pus in the floor of the pelvic cavity. A perforation could not be detected in the vaginal vault either from within the vagina or from the pelvic cavity, nor in the uterus, which was somewhat enlarged, softened and covered

with a dirty yellowish exudate. Both tubes were intensely congested, but free pus could not be "milked" from the patent fimbriated ends. On the anterior surface of the liver were two softened depressed areas, irregular in outline, produced by collections of inspissated pus. A thin film of pus covered the surface of the liver. The stomach was much distended and filled with a turbid, brownish fecal fluid. In the left dome of the diaphragm was a ragged ulcerated area, about 7 cm. in extent. In the center of this was a perforation about 2 cm. in diameter.

The left side of the chest was filled with a brownish, turbid, foul-smelling fluid, completely filling the left pleural cavity, compressing the lung and forcing it closely against the mediastinum. Fluid could be made to flow back and forth through the diaphragmatic opening, as the lung was forced down into the fluid.

COMMENT

Perforations of the diaphragm practically always result from subphrenic abscesses. These in themselves are not particularly uncommon, but perforations occur, probably, in less than one third of the cases. Lang,[1] in a series of 173 cases, found 67 perforations, or 35 per cent; while Martinets,[2] in 138 subphrenic abscesses found only 33 perforations, or 25 per cent.

The site of the perforation varies, of course, with the situation of the abscess. According to Barnard,[3] abscesses may occur in six locations: four intraperitoneal and two extraperitoneal. The commonest abscess is probably the right anterior intraperitoneal, between the convexity of the right lobe of the liver and the dome of the diaphragm and between the falciform and right coronary ligaments of the liver. Subphrenic abscesses on the left side occur less frequently, although the left anterior intraperitoneal, corresponding to the pouch of the left kidney, seems to be second in order of frequency. It usually results from suppuration of the left lobe of the liver or a perforated gastric ulcer. The third commonest site is the right extraperitoneal, in the uncovered space between the coronary ligaments of the liver; such an abscess is almost always a result of intrahepatic suppuration. The right posterior intraperitoneal location, corresponding to the pouch of the right kidney, is also a frequent location for subdiaphragmatic abscess. Large quantities of pus may collect here before emptying into the general peritoneal cavity or right anterior intraperitoneal space of Barnard. Abscesses in either of these locations most frequently result from appendical or pelvic inflammatory conditions. The left posterior intraperitoneal abscess is rare and confined to the lesser peritoneal cavity. The left extraperitoneal abscess of Barnard is located near the left kidney, and like the left posterior intraperitoneal abscess, rarely occurs.

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1. Lang, quoted by Osler and McCrae: Osler's Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1925, vol. 3, p. 944.

2. Martinets, quoted by Osler and McCrae (footnote 1).

3. Barnard: Brit. M. J. 1:371, 1908.

Clinically, subdiaphragmatic abscesses have been divided into gaseous and nongaseous, because of the different clinical pictures presented. While this division may be of help from a clinical standpoint, its usefulness from a pathologic point of view is questionable, for the same etiologic factor may in one instance produce a gaseous and in another a nongaseous abscess. For example, a perforated gastric ulcer may produce a gaseous abscess resulting from swallowed air, while in another patient gas may not be present; or appendical abscesses, which are generally simple and nongaseous, may contain air as a result of bacterial activity.

In case 1 there was a typical perinephritic abscess. It differed from the usual abscess in this location, because it did not perforate the diaphragm in the right anterior intraperitoneal space of Barnard, below the right anterior coronary ligament of the liver. It formed, however, a second subdiaphragmatic abscess between the layers of the coronary ligament in the right extraperitoneal space, a space usually occupied by a subphrenic abscess resulting from intrahepatic suppuration.

Case 2 illustrates an extensive retroperitoneal inflammatory process resulting from a retrocecal appendix and perforating the diaphragm in its extraperitoneal portion. This case is unusual in that there were no signs of inflammation in the true peritoneal cavity, apart from a paralytic ileus, although a rather extensive inflammatory and necrotic process had been present within the abdomen for a month.

Case 3 is the first instance of its kind that has come to my attention in which the diaphragm was perforated during the course of an acute generalized suppurative peritonitis. In long-continued cases of intraperitoneal suppuration, it is not unusual to have secondary foci set up in the pleural cavity by extension through the lymphatics or blood stream; but appreciable losses of diaphragmatic substance with large or small perforations occurring during an acute generalized peritonitis are most uncommon. This case could not rightly be termed a case of subphrenic abscess, for the condition was extensive throughout the abdomen. Perforation of the diaphragm had occurred in the left anterior intraperitoneal space of Barnard in the dome of the left side of the diaphragm.

In a search through the medical literature, I have been unable to find a similar case reported. It is a condition of such uncommon occurrence that it is not mentioned as a possible complication of peritonitis in standard works of medicine and surgery (Osler's System of Medicine, Keene's System of Medicine, and others). The evident rarity of its occurrence accounts for these brief case reports.

ACUTE APPENDICITIS

WITH A REPORT OF ONE THOUSAND CONSECUTIVE CASES*

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This contribution to the subject of acute appendicitis is based on a study of 1,000 consecutive cases in which operation was performed by members of the Quain and Ramstad Clinic, Bismarck, N. D., from November, 1919, to September, 1927. The report, submitted herewith in tabulated form, has been compiled by one of us (R. H. W.) after a careful review of our clinical histories. It is hoped that the results obtained by our particular methods of treatment may be of some interest and use to those who may wish to make a larger review of the whole subject of acute appendicitis. It should be stated that the report is submitted, not in any spirit of superior wisdom or skill, but rather with a sense of humility because we have so often failed to save human life. A study of the report will demonstrate that with better surgical judgment there would have been fewer deaths.

The lessons in diagnosis that we gained and the problems of postoperative management that we encountered in this series will not be mentioned, but the more important features of the operative technic and the final results will be discussed briefly.

From a study of recent publications on acute appendicitis—fewer now than ten or fifteen years ago—it is evident that as yet not all surgeons follow the same tactics in combating the disease. It is evident, also, that there has not been any abatement in the frequency or in the mortality of the disease. Indeed, a few articles have been presented by medical statisticians to prove that in the past few years there has been an increase in the mortality rate from appendicitis in this country. The reasons for this have not been satisfactorily explained. Whether the increase is real or only apparent, we must leave without discussion. The fact that one cannot successfully prove the statement false should be a matter of serious consideration to all who are actively trying to reduce the mortality of appendicitis.

Recently collected figures from the Bureau of Vital Statistics indicate that about 25,000 people die annually in the United States from acute

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appendicitis. This signifies that there has been an increase of 30 per cent in the mortality of this disease within the past decade and it means that as many people die from appendicitis each year as from ectopic pregnancy, pyosalpinx, gallstones, and pancreatic, splenic and thyroid gland disease combined. These figures, even if only approximately correct, suggest that no member of the surgical profession has a right to rest on the laurels of his record in cases of appendicitis, no matter what they be, but rather that he should be urged to a more intensive study of the whole problem of acute appendicitis.

Many writers seem to gage the severity and prognosis of a given case of appendicitis entirely by the length of time between the onset of the attack and the operation. In the majority of cases this relationship between cause and effect is undoubtedly present, yet there are many cases in which the appendix will be in a state of acute inflammation for several days before it becomes surrounded by infectious exudate. There may be a milky exudate of considerable quantity, but a culture of it will often prove it to be sterile. In many cases of this type healing occurs promptly after appendectomy and without marked inflammatory reaction. It does not seen fair to include such cases among those of late appendicitis or peritonitis. They belong essentially to the class of uncomplicated acute appendicitis even if three or more days have elapsed since the first symptom appeared.

Again it happens not infrequently that gangrene occurs early and that the cultured exudate is found to be infectious in much less time than the forty-eight hours usually mentioned as an arbitrary time limit between a clean and an infected peritoneum. Free and virulent pus has been encountered on many occasions in less than twenty-four hours after the acute symptoms began.

The true extent of the pathologic process present in any given case cannot be definitely known until the incision has been made. With the pathologic process before his eye, the surgeon should judge by what he sees and feels in each case rather than by what he remembers about the time of onset, and he must base his method of treatment on the judgment he forms concerning the degree and extent of the infection.

Having adopted a classification on this principle, we have divided the 1,000 cases into three groups:

Group I, acute appendicitis; group II, acute appendicitis with abscess, and group III, appendicitis with progressive peritonitis.

The first group includes all cases in which the surgeon was reasonably sure that there was as yet no infection of the surrounding peritoneum. In many cases which were placed in this class the appendix showed gangrenous areas, was covered with fibrin or was

adherent to surrounding structures. In some instances, considerable exudate was present. A small temporary drain was inserted after appendectomy in all such doubtful cases. This drain was removed the next day, when the appearance of the wound, or culture taken at the time of operation, showed that there was no infection. A few patients in this group had a remission of symptoms when first seen and for that reason were not operated on until two or three days later, usually after a recrudescence of pain. Subacute and interval cases are not included. There were 551 cases in this group, with two deaths.

When the infection was believed to be distinctly localized, either as a walled-off abscess, or definitely confined to the vicinity of the appendix, the surgeon classified the case as appendicitis with abscess. This group included 289 cases, with seven fatalities.

The remaining 160 cases were placed in the class of appendicitis with progressive peritonitis, because there was no question at the time of operation as to the free and spreading infection. Eighteen of the 160 died, yet the cause of death in some of these was only remotely due to appendicitis, as will be explained later.

Discrepancies have no doubt occurred in our efforts to differentiate "abscess" or "localized" peritonitis from "progressive" peritonitis. It is sometimes difficult to judge correctly and quickly whether one is dealing with a large localized infection, or with a free and spreading peritonitis. Practically, it is unimportant, and no time or effort should be wasted in trying to settle the question. The main surgical treatment is the same in the two conditions, and the operative technic later described has been followed in both classes of cases.

All patients with acute appendicitis received in our service were operated on at once after diagnosis was made and consent was obtained, with two exceptions. In one case, consent to the operation was withheld; in the other, the patient was moribund. Both patients died and their cases are not included in this report. A small number were first seen when the attack was subsiding. In these, interval operation was usually made—which excludes them from present consideration.

METHOD OF OPERATION

Some years ago we attempted to follow a different line of treatment, based on the recommendation of Dr. Ochsner, in cases in which an abscess was forming and in which the infection appeared to be localized. This plan was abandoned after several unfortunate experiences and after learning of the excellent results obtained by Knott who reported several hundred cases of abscess in which immediate appendectomy had been performed with a hitherto unheard of low mortality. It has been our practice, therefore, during the entire time of this report, to hurry the

patients to the operating room practically without preliminary treatment, with a conviction that the patient's best chance for recovery lay in the quickest possible removal of the appendix and the establishment of efficient drainage from the infected peritoneum. It should be stated in this connection that acute appendicitis has been considered an emergency of first importance over which neither the pressure of office hours nor the surgeon's rest at night has been allowed to take precedence. As a matter of fact, the majority of these operations were made in the hours between sunset and sunrise.

Nitrous oxide and oxygen gas anesthesia has been used in most of our work. A small amount of ether has been added occasionally. In all serious surgical risks, an infiltration of 0.5 per cent solution of procaine hydrochloride has preceded the abdominal incision. Practically all secondary enterostomies have been made with local anesthesia.

We do not use lateral, longitudinal incisions in the abdominal wall for any purpose, and can see no valid reason for the use of the right rectus incision in surgical intervention in appendicitis. We practice the so-called split muscle incision, and in the few instances in which the mere splitting gives too little room, the incision is enlarged by cutting across the linea semilunaris. The separation of the aponeurotic fibers may then be continued and, if need be, a section of the rectus may be severed. A second split muscle incision near the left groin is made when needed for additional drainage or for immediate enterostomy.

When the surgeon unexpectedly encounters a posterior appendix, he may sometimes find his split muscle incision too low for the necessary ligations of high blood vessels. The incision through the skin and external oblique is then extended upward, and the deeper muscles and the peritoneum are split at a higher level. This double opening is much more conservative of anatomic structure than the practice of cutting across muscle and nerve fibers.

We know from experience that sufficient room for the required surgical procedure under discussion is practicable through split muscle incisions. We also know that in virulent infections the abdominal wall suffers permanent damage in proportion to the operative damage inflicted at the time of operation.

We believe that the low percentage of postoperative hernia in our series is another distinct benefit derived from the conservative incisions. "Follow-up" inquiries have disclosed but fifteen incisional hernias up to date, or 1.5 per cent. Only eleven of these caused sufficient trouble to bring the patient back for herniotomy. It is interesting that the only patient on whom a modified right rectus incision was made returned with a hernia.

Before the peritoneum is opened, when pus is expected, the exposed tissues are covered with pads in order to minimize contamination of the wound. By protecting the wound in this manner, a few sutures may safely be placed in clean tissues, with separate instruments, at the completion of many operations, even after pus has been found and evacuated.

The practice of holding up the edges of the peritoneum with forceps during the removal of an infected appendix (or any other operation) is a bad habit. Harmful bruising of the serosa is unavoidable.

After an abscess or infected area is opened, the exudate is promptly aspirated and the cavity gently cleansed. Too careful "walling off" of the infected area by the introduction of gauze pads will do more harm to the peritoneum and to the patient than the simple and quick withdrawal of the gross exudate by suction and trusting the rubber drains later to undo any possible spreading of the infection during the operation. When retraction of omentum, cecum or intestine is required, a smooth metallic spatula in a steady hand does the least damage.

The index finger is next introduced to locate the appendix. If the appendix is hard from infiltration or distention, or presents a large segment into the cavity, it is easily found. But if the appendix has been gangrenous for some time, has become soft and collapsed, or is embedded some distance away from the main pus cavity, it may tax the most experienced finger to determine its location and to liberate the sloughing remains without doing too much violence. The exploring finger must first be able to tell where the appendix is not. This is concluded from the comparative softness of the wall of the abscess and from the easier give in the surrounding tissues. As soon as the location and direction of the appendix is determined, it is gently dissected free by the same finger. Whenever possible, instruments should be avoided for this purpose. When the finger fails to locate the offending organ, a gentle traction of the wound will usually suffice to expose the head of the cecum, from whence come the required landmarks. Traction should not be made on the cecum nor on any other viscus. Violation of this rule may provoke destruction of the protecting infiltration, and dissemination of infection.

After the appendix is liberated sufficiently, the meso-appendix is tied off with catgut on short intestinal needles. It is important that the ligation be done in the depth of the wound without causing traction on the meso-appendix. It should be remembered that next to the appendix the meso-appendix is the greatest source of spreading infection. Septic thrombi are easily dislodged, and these give rise to pylephlebitis, and multiple abscesses of the liver, which are usually fatal.

No effort should be made to cover up the stump in the cases under discussion. It should be tied off and left, or in the presence of serious

distention, a small rubber tube may be passed through it into the cecum. Fear need not be entertained about the possibility of a resulting fistula. Such fistulas soon heal and are serviceable while they last.

Cigaret drains of soft dental rubber are much better, in our opinion, than rubber tubes. A gauze tampon, surrounded by rubber, may occasionally be required over a deep bleeding area. The amount of drainage material used should be large when the peritoneal infection is extensive. Ten or a dozen long and soft rubber cigarets have frequently been inserted. Two or three rubber gloves, sometimes packed with gauze wicks, have been placed in the pelvis to hold the intestine away and to aid the exudate in finding an easier path to the outside. This is in line with Lennander's teaching of many years ago. He advised that in acute peritonitis the most important part of the treatment was to "lay the infected peritoneum extraperitoneal." The immediate storm is usually over in two or three days, and then the quantity of drainage material can be reduced rapidly by withdrawing one or more cigarets at each dressing. When a large quantity of rubber is used, there is not likely to be as much difficulty in its removal as when one or two small cigarets become entangled deep in the abdomen.

The incision should be placed low enough so that the drainage material rests against the parietal peritoneum externally and in the pelvis. This is for the purpose of minimizing the extent and amount of intra-abdominal postoperative adhesions. The suppurating tract, gradually decreasing in diameter, as the cigarets are withdrawn, will be composed of visceral adhesions on its mesial side only. We have operated on a number of patients for obstruction of the bowel, both chronic and acute, because at some previous operation a discharging sinus and later fibrous adhesions had been allocated entirely within the abdomen with free and open peritoneal cavity all around.

In order to shorten the intra-abdominal length of the discharging sinus, we have on many occasions and with much satisfaction placed the edges of the peritoneum as deeply as possible along the rubber drains. This is easily done by packing loosely an iodoform strip or a rubber cigaret between the peritoneal margin and the transversalis muscle. In children and in adults with shallow ileocecal fossae, it is sometimes possible to fasten the mesial side of the peritoneal wound to the posterior peritoneum over the psoas muscle with a catgut stitch. This method is especially useful when the abscess is located within the pelvis. The peritoneal flap pushes intestinal loops away from the drainage material, and the exudate becomes extraperitoneal as soon as it reaches the brim of the pelvis.

In most cases in which there is a strictly localized abscess, the gangrenous or perforated part of the appendix is usually in free communi-

cation with the main abscess cavity. An incision into the abscess in such cases will drain the infection directly from the original focus as well. But the appendix is somewhat of a rover, and the farther from its normal habitat it has taken up its residence, the more apt it seems to be to get itself into trouble and to cause trouble. One finds, therefore, the most serious complications when the gangrenous appendix is located in the middle of the abdomen or behind the cecum.

In our experience, the former situation is the most deadly. At the beginning of the attack, adhesions begin to form between the mesenteries and loops of the small intestine, and obstruction of the bowel complicates the infection from the start. The abscess or abscesses form along the mesentery, and it may be humanly impossible to open and establish efficient drainage to every infected nook and side chamber before the final review on the autopsy table. We have encountered serious retrocecal infections less often. There have been but three cases of subphrenic abscess in our series. This danger has always been kept in mind, and special efforts have been given to the placing of drainage after every retroperitoneal appendectomy.

The abnormally located appendix seems to be most apt to produce multiple pus pockets of irregular outlines, but usually communicating with one another. In such cases, it does not suffice merely to drain one pocket and stop. The appendix may be some distance away from the abscess first found near the abdominal wall. The partial release from intra-abdominal pressure may close the communicating sinus from the appendix to the opened abscess cavity, and the fire continues to smolder in its concealed furnace. We have therefore found it advisable to adopt the following working rule: The more concealed a suppurating appendix is and the harder it is to find, the more important it is for the patient's welfare and for the surgeon's mortality records that this appendix be found, removed, and the place whence it came, drained.

While we believe in the principle that it is to the patient's best interest to have the acutely inflamed appendix removed as the first step in treatment, irrespective of the extent of the peritoneal infection, it is not recommended that every physician who assumes the responsibility of operating for acute appendicitis should consider it his duty to remove the appendix in all cases of abscess—far from it. The "occasional operator" may glory in his ability to find and remove every "cold" appendix for which he makes a search, but he should refrain from spending time and energy in trying to locate a gangrenous appendix securely hidden in some concealed niche of a densely infiltrated and suppurating wall of adhesions. It would prove disastrous to many of his patients, if he were to do so before he has gained a tactile familiarity with the various fixtures in the abdomen and before his finger has learned to enucleate an

adherent appendix without seeing it. Until sufficient experience has been reached, the best results will follow the least possible manipulating after the pus flows freely.

In the presence of intestinal distention and obstruction the surgeon must judge whether or not an immediate enterostomy should be performed. When the infection is widespread, the distention great and reverse peristalsis evident, enterostomy should be performed at once. If the peritoneal infection is only of a few hours' duration and the distention moderate, enterostomy may not be required. No rule can be formulated, as each case becomes a law unto itself. But it should be remembered that a properly made temporary opening into the intestine does not injure any of these patients, and that it is the only salvation for many. We have never regretted performing a primary enterostomy; we have often regretted its postponement.

It is best not to place the enterostomy tube, or tubes, in the operative wound. We have found it preferable to perform this supplementary operation in a second split muscle opening, near the left groin or flank, with a fold of the omentum or a loop of the pelvic colon as a protection to the intra-abdominal part of the sinus.

Enterostomy was performed at the time of primary operation in thirty-one cases in our series; it was made at a later seance in thirty-eight. In a number of patients it was necessary to reoperate, one or more times, thus producing three or even four artificial openings. With a few exceptions, the sinuses closed spontaneously.

The draining of an exudate from any cavity takes place most quickly and efficiently if the cavity is opened at the bottom. The advisability of opening an abscess at its lowest point was known in ancient times. This principle holds true also when it is desired to drain an infected peritoneum through an opening in the anterior abdominal wall. Our patients have made safer, quicker and more comfortable recoveries since we learned to place them in bed in such a posture that the open wound is at the lowest point of the abdominal cavity. An abundance of pillows is placed on the bed and the patient is made to lie on his abdomen with the thorax elevated and the knees drawn up. It is essential that this posture commence immediately after the operation—when possible even on the cart from the operating room—in order to turn gravity in the right direction and at the time when it is most effective. An additional benefit from the ventral posture comes from the fact that the stomach and duodenum have less difficulties with retention and regurgitation, and the patient will be tortured with the stomach tube less often.

In spite of much effort to instruct both the public and physicians about the danger of giving laxatives haphazardly in acute abdominal lesions, castor oil, magnesium sulphate, and their equivalents, continue

to aggravate and complicate acute appendicitis. The great majority of all the severe cases we have seen, including practically all the patients who had early and hopeless peritonitis, had been given a cathartic soon after the onset of the disease. One may forgive an overzealous mother who tries to do the best she can, but it is most distressing to see medical men of modern education still addicted to the medieval and pernicious habit of prescribing cathartics when they are as plainly contraindicated as they are in acute appendicitis.

POSTOPERATIVE RESULTS

We believe our results give several definite hints as to the advisability of removing the appendix at the primary operation. Appendectomy was performed in 262 of the 289 cases of abscess, leaving twenty-seven in which drainage was established without removing the appendix. In several of the cases in which appendectomy was not performed, drainage was obtained through the vagina; in others there were complicating diseases which were assumed to contraindicate all operative procedures beyond a simple incision and draining of the abscess. But in the majority of these cases, the appendix was left behind, because the surgeon was unable to locate it without too extensive manipulations and expenditure of time. The postoperative complications were proportionately greater in the twenty-seven than in the rest of the group. A much longer period of hospitalization was necessitated by the prolonged suppurations which usually followed a nonremoval of the appendix. Most of the secondary abscesses and additional operations for their relief and nearly one half of the postoperative enterostomies for obstruction of the bowel were among these same twenty-seven. The appendix had not been removed in three of the seven cases of abscess in which death occurred.

The two patients in the group of cases of peritonitis from whom the appendix was not removed died from toxemia soon after the drainage operation. Their desperate condition could not have been improved by any form of technic. We feel convinced, however, from a comparison with earlier experiences in progressive peritonitis that a ruptured appendix remaining in the abdomen after a simple drainage operation acts as a potent feeder for further extension of infection and complications. When the cause of the infection is removed, the patient has a better chance to overcome the damage already wrought on the peritoneum.

The following conditions were outstanding and instructive among the patients who died:

A boy, aged 10, who died from multiple abscesses of the liver after the removal of a rather mildly inflamed appendix without abscess, proved

the necessity of handling an edematous meso-appendix with the utmost care. The other death in the simple acute cases was that of a child with respiratory infection who developed pneumonia after the operation.

Two of the deaths listed under appendicitis with abscess were indirectly due to a complication with incarcerated hernia and mistaken diagnosis. A woman, aged 60, with a frequent temporary incarceration of a large umbilical hernia, entered the hospital several days after one of her attacks of midabdominal pain. The hernial mass, as well as the whole right side of the abdomen, was hard and tender. At operation, incarcerations of omentum and colon were replaced, and an inflamed appendix and an abscess were discovered. The abscess was drained; the appendix was not removed. General sepsis and death followed. The second hernial complication was found in a young man who gave a history of occasional attacks of pain and distention in a right inguinal hernia. Four days after the beginning of such an attack, he entered the hospital with a large bulging mass in the inguinal canal. It was opened and found to contain pus, masses of fibrin and an incarcerated omentum. Drainage was instituted through the hernial sac, and the abdomen was not explored. He died from peritonitis five days later and two days after a gangrenous appendix had been discovered as the cause of the infection. One patient with chills, both before and after the operation, died three weeks later from multiple abscesses of the liver.

In the group of cases of peritonitis, it should be noted that of the eighteen patients who died, two were men, 59 and 62 years of age, both of whom had complicating cardiorenal inefficiency. Preliminary gastric lavage is very difficult in children, and aspiration of fecal vomitus during the operation and consequent pulmonary consolidation was the determining factor in the death of a child. Three had delirium and hyperpyrexia (over 105 F.) before operation. One showed gangrene of the entire cecum at the autopsy. One had a serious secondary suppuration of the parotid glands, and one suffered an extrusion of the bowel a few hours after operation. The majority of the patients with peritonitis who died did so within two or three days after operation with symptoms of a continuation of the toxemia and of insurmountable obstruction of the bowel.

One patient, a young man, committed suicide after he had entirely recovered from his operation and was ready to go home, and another man, aged 60, died suddenly—probably from embolism—following an intestinal resection two months after the original operation for peritonitis. Strictly speaking, neither of these died from appendicitis, and it is doubtful whether they should be included in the mortality list. With these two cases excluded, the number of deaths was twenty-five, or an average mortality of 2.5 per cent in the 1,000 cases of acute appendicitis.

Grouping of 1,000 Cases of Acute Appendicitis According to Extent of Peritoneal Infection

* Group I includes cases of infection confined to the appendix; group II, abscess, and cases with peritoneal infection restricted to immediate neighborhood of the appendix (i. e., early stage of progressive peritonitis), and group III, cases of diffuse and progressive peritonitis.

	Group I	Group II	Group III
Total number of cases	551	289	160
Appendectomy made in	551	262	158
Appendectomy not made in	0	27	2
Died	2	7	18
Age of Patients			
Youngest	4 years	1½ years	3 years
Oldest	60 years	67 years	62 years
Average age	21 years	29 years	20 years
Time of Operation after Onset			
Shortest	½ day	1 day	1 day
Longest	11 days	35 days	21 days
Average	2½ days	4½ days	3½ days
Duration of Drainage			
Shortest	1 day	2 days	5 days
Longest	20 days	120 days	60 days
Average (of those drained)	2 days	12 days	15 days

Major Postoperative Complications

Group I	Group II	Group III
Pneumonia 5	Intestinal obstruction (secondary) 22	Intestinal obstruction (secondary) 16
Cholecystitis 3	Enteritis 5	Enteritis 6
Phlebitis 2	Secondary abscess 5	Pneumonia 3
Pylephlebitis 1	Peritonitis 4	Abscess of abdominal wall 3
Pyosalpinx 1	Phlebitis 4	Postoperative hemorrhage 2
Ovarian cyst (large) 1	Hernia incarcerated 2	Subphrenic abscess 2
Abscess of the abdominal wall 1	Pneumonia 2	Phlebitis 2
	Pylephlebitis 1	Abortion 2
	Subphrenic abscess 1	Otitis media 2
		Parotiditis 1
		Abscess of the lung 1

Secondary Operations

Reopen wound for infection 3	Enterostomy (including 7 primary) 29	Enterostomy (including 24 primary) 40
Cholecystectomy 2	Secondary abscess 6	Closure fistula 5
	Closure fistula 5	For infection of abdominal wall 3
	Appendectomy 5	Thoracotomy 2
		For postoperative hemorrhage 1

Mortality

Pneumonia 1	Intestinal obstruction 2	Toxemia (within 36 hours after operation) 6
Multiple abscesses of the liver 1	Hernia and peritonitis 2	Intestinal obstruction 6
—	Peritonitis 1	Pneumonia, lobar 1
Total 2	Subphrenic abscess 1	Pneumonia, aspiration 1
(0.36%)	Multiple abscesses of the liver 1	Gangrene of cecum 1
	—	Intestinal extrusion 1
	Total 7	Embolism (2 months after recovery from appendectomy) 1
	(2.42%)	Suicide 1
		—
		Total (minus last two) 16
		(10%)

Average mortality in 1,000 cases, 2.5%

THE POSTOPERATIVE PROGNOSIS OF CANCER OF THE BREAST

REPORT OF A SERIES OF CASES STUDIED WITH REFERENCE TO THE RAPIDITY OF PROGRESS OF THE GROWTH PREVIOUS TO THE TIME OF OPERATION

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The end-results so far obtained in fifty-six patients with carcinoma of the breast on whom I have operated during the past twenty years are summarized in tables 1, 2 and 3. Except in case 40, all operations were typical complete excisions including the removal of the pectoral muscles and axillary glands. In all but four of the more advanced forms, sections were cut of the primary tumor and lymph nodes. Each patient has been traced either to date of death or to the condition at present, that is, in June or July, 1927.

In checking the results obtained in this small group of cases, I have reviewed most of the literature dealing with the late results following operations for cancer of the breast which has been published during the past fifty years. While opinions expressed in this paper will be based on the results observed in my own small series of cases, these opinions have in each instance been checked against the mass of data compilable from other sources.

The cases here reported have been grouped into three tables corresponding to the classification adopted by the Departmental Committee on Cancer of the British Ministry of Health.

Table 1 contains cases from class 1 of the British classification, i. e., cases in which, so far as could be ascertained, the growth was entirely confined to the breast, the axillary glands not being invaded.

Table 2 contains cases from class 2, in which the axillary glands were already invaded but in which there was no evidence of involvement of any other contiguous or distant organ or tissue.

Table 3 contains cases from class 3 in which either the adjacent or distant organs or tissues were involved, e. g., the pectoral muscles, the skin when ulcerated, the cervical glands, the opposite breast, etc.

My records show that fifteen cases belong in class 1, namely, cancers of the breast confined to the breast without demonstrable involvement of the axillary glands. As in other reported series, the results are, on the whole, gratifying. Eleven of the fifteen patients are still alive and free from recurrence. Six of the seven operated on more than ten years previously have lived from eleven to fifteen years after operation. Five of the six are still living, and one died of cancer fifteen years after operation.

In general, statistics covering cases from group 1 show from 80 to 90 per cent of five year "cures," and the English statistics show 90 per cent of ten year cures in the Leeds series. My group shows 83 per cent of five year cures. Statistically, my group 1 is possibly skewed by the inclusion of cases 5 and 40. In case 5, the patient died in a manner similar to that observed in class 2, group A. My records fail to mention axillary metastases, but the rapid fatal recurrence would seem to indicate that there were metastases that were not found or recorded. In case 40, operation was performed under the diagnosis of Paget's disease. Because of advanced mitral stenosis, a complete radical amputation was not attempted. The local recurrence was a typical scirrhous cancer.

As a rule these patients in class 1 come to operation at a relatively early period following the discovery of the tumor, but the variation in

TABLE 1.—*Data of Cases in Class 1*

Case Number	Preoperative Time, Months	Postoperative Time, Months	Present Condition
52	2	16	Satisfactory
46	¼	28	Satisfactory
48	1	24	Satisfactory
39	12	60	Satisfactory
30	¾	84	Satisfactory
26	1½	108	Satisfactory
40	6	60	Recurrence
24	1	84	Died of cancer
19	?	132	Satisfactory
18	?	132	Satisfactory
13	½	162	Satisfactory
7	?	180	Died of cancer
10	?	180	Satisfactory
5	4	19	Died of cancer
11x	3	168	Satisfactory

time of from one week to twelve months is so great as to make the average, three months, of little statistical significance. The English series shows a mean duration previous to operation of more than six months.

It is not necessary to comment further on results in class 1. If all cancers of the breast could be operated on before glandular involvement, this disease would be largely conquered.

My series comprises thirty-one cases in class 2. The results in this class present a sharp contrast to the generally satisfactory results shown in cases in class 1. Of twenty-one patients operated on five or more years ago, only six were alive at the end of five years and three of the six died later of cancer. My results in cases in class 2 have been essentially similar to those reported by other surgeons the world over.

In the past, all physicians were inclined to credit such results as are shown in cases 14, 16 and 35 to the thoroughness of the operative

technic. I am more than half inclined to suspect that some day it will be found that these results are due to factors about which, as yet, little or nothing is known.

To suggest a line of investigation which may help to estimate the benefits, if any, to be expected in operations in cases in class 2, I have subdivided my cases into groups A, B and C. Group A is composed of what may be conceived clinically as highly malignant cases, because within four months or less after the discovery of the tumor more or less extensive axillary involvement was found at operation. Cases in

TABLE 2.—*Data of Cases in Class 2*

Case Number	Preoperative Time, Months	Postoperative Time, Months	Present Condition
Group A			
50	1	18	Satisfactory
51	1	8	Died of cancer
53	1	6	Died of cancer
45	4	18	Died of cancer
42	1½	37	Satisfactory
37	1	8	Died of cancer
34	1½	36	Died of cancer
32	2	8	Died of cancer
35	1½	72	Satisfactory
29	4	12	Died of cancer
22	3	3	Died of cancer
23	2	23	Died of cancer
14	4	146	No recurrence
12	3	42	Died of cancer
8	3	36	Died of cancer
2	4	108	Died of cancer
Group B			
20	6	24	Died of cancer
41	6	48	Recurrence
44	6	24	Satisfactory
47	12	24	Satisfactory
49	8	24	Satisfactory
43	12	30	Satisfactory
27	10	48	Died of cancer
16	24	84	Died of cancer
21	24	36	Died
15	12	24	Died of cancer
11	15	60	Died of cancer
Group C			
33	36	13	Died of cancer
28	30	108	Satisfactory
4	60	5	Died of cancer
3	48	66	Died of cancer

group B are arbitrarily suspected of being less malignant than cases in group A because, although glandular metastases may actually have been present as early as four months after the discovery of the tumor, there was on the whole an element of insidiousness about them that did not promptly force them to operation; when encountered from six months to two years after the tumors had been discovered, they still definitely belonged in class 2. Group C is conceived to be made up of cases showing a low grade of malignancy. This is justified by the fact that from two and a half to five years after the discovery of the tumor, they still belong in class 2.

Group A is of particular interest so far as it illustrates how in operations for cancer the term "early" cannot be defined in terms of time. This group is composed of sixteen cases in all of which operation was performed within four months of the discovery of the tumor. The average interval is 2.3 months or approximately nine weeks as compared with about thirteen weeks in the cases in class 1. The distinguishing feature of group A is that each case did show metastases of the axillary glands at the time of operation. Irrespective of any potentially malignant characteristics lurking in the individual tumors comprising class 1, not one of them had up to the time of operation demonstrated the capacity of producing early glandular metastases. In group A, on the other hand, each individual tumor demonstrated malignancy of a degree capable of producing axillary metastases in less than four months and in most of the cases in less than two months following the discovery of the tumor.

TABLE 3.—*Data of Cases in Class 3*

Case Number	Preoperative Time, Months	Postoperative Time, Months	Present Condition
38	60	36	Died of cancer
36	12	6	Died of cancer
31	156	36	Died of cancer
25	4	30	Died of cancer
17	36	6	Died of cancer
9	42	60	Died of cancer
6	24	22	Died of cancer
1	12	2	Died of cancer

The literature on cancer is filled with statements to the effect that early operation is the one most important factor if a cure is to be obtained. To the laity and probably to most physicians, this term signifies some relationship measurable in intervals of time. Usually, it is taken to mean that a short interval has elapsed between the first discovery of a lump in the breast and the time of operation.

That this time interval is not per se a dominant factor in regard to postoperative prognosis is readily shown by comparing the results obtained in cases in class 1 with those shown for group A of class 2.

The cases in class 1 were "early" cases, the term being used in a purely anatomic and pathologic sense, but they were not necessarily particularly early in the sense of time interval. The cases in class 2, group A were, however, all early cases in a sense of time interval; in all the cases, operations were performed within four months of the discovery of the tumor; the average time interval was only about nine weeks, and yet this group is the worst of all groups as regards prognosis. These cases in group A all showed axillary metastases at an early stage in the growth of the tumor. That this early metastasis actually

indicates a high grade of malignancy is, I believe, shown by the results in this group. Of the sixteen patients in this group, twelve are dead with an average postoperative life of only 2.14 years (or not quite two years and two months). Even this average is somewhat skewed by the presence of one patient who lived nine years after operation. This woman had extensive skin recurrences four years after operation. For some reason, these recurrent tumors regressed, and she remained comparatively well until shortly before her death nine years after operation. Four patients still survive twelve years and two months, six years, three years and one month and one year and six months after operation. The two patients still alive and free from demonstrable recurrences twelve years and two months and six years, respectively, after operation are the only ones in this group so far in whom operation seems to have prolonged life. I have never been able to account for the result in case 14, in which the patient was still alive twelve years and two months after operation. At the time of operation, a woman, aged 43, had an apparently rapidly growing, rapidly metastasizing tumor. I thought the prognosis was especially bad. Thirteen months after operation, she gave birth to a child which she nursed on the remaining breast. For the past three and a half years the right arm has been enormously swollen, but I have never been able to demonstrate any recurrence of the cancer, and her general health has remained good.

Group B of class 2 is composed of cases in which the patients came to operation between six months and two years after the discovery of the tumor. For reasons already given, this group is conceived of as being composed largely of only moderately malignant cases. If so, irrespective of any life-prolonging effects from the operation, one might expect a longer average postoperative period of survival than that obtained in cases in group A. Actually, the deaths occurred in this group 3.86 years after operation as compared with 2.12 years after operation in the cases in group A, and there was a total survival before death of nearly five years in cases in group B compared with less than two and a half years in cases in group A.

Group C of class 2 contained four cases in which operation was performed from two and a half to five years after discovery of the tumor. That they in general represent instances of a relatively low grade of malignancy is proved by the fact that even at the late period at which operation was performed they still remain in class 2. For the reasons already suggested in discussing classes A and B, one might expect, *a priori*, that some of these cases would show relatively long periods of postoperative survival irrespective of any question of complete or permanent cure. Small as this group is, it nevertheless contains two such examples. In case 28, operation was performed two and a half years after the discovery of the tumor, and the patient was

apparently free from recurrence and in good health in June, 1927, nine years after her operation. In case 3, the patient had cancer of both breasts with the older tumor discovered four years before the date of operation. She died of cancer, but she remained in apparently good health for nearly five years after her operation and survived a total of nine and a half years after discovery of the cancer in the first breast. This small group again serves to confirm the impression concerning the enormous importance of that undetermined factor which is designated as the malignancy of the disease.

Our series contains only seven cases of the class 3 group in which the tumor had invaded tissues other than the breast and axillary glands. In this little group, the total survival periods range from fourteen months to sixteen years. In a study of the individual cases, I cannot find any reason to infer that operation prolonged the life of any patient in this group. Without exception, those patients with growths of such a degree of malignancy as to place them in class 3 in a short time died within a few months after operation. Generally speaking, those patients who took years to reach a condition that would place them in class 3 also lived several years after the operation.

CONCLUSIONS

Throughout this study, both in regard to my own cases and those reported by other surgeons, I have been forced to the conclusion that the ultimate prognosis in the individual case is, for the most part, determined by the degree of malignancy of that woman's own tumor. The woman who happens to be fortunate enough to have a thorough operation performed for a slowly metastasizing tumor before glandular involvement has taken place stands from eight to nine chances out of ten of remaining permanently cured. Surgery has little to offer to the woman with a rapidly metastasizing tumor, because even though she is operated on almost immediately after the tumor is discovered, she will probably die within a relatively short period after operation. In the case of the slow growing, less malignant tumors, even though operation is performed at relatively late periods, the period of post-operative survival is liable to be prolonged in keeping with the course of progress indicated previous to the operation.

Surgeons and pathologists seem to be in accord in the opinion that the final prognosis in the individual case, in which operation was performed for cancer of the breast, is largely dependent on the degree of malignancy of the particular tumor under consideration. There is nothing new or modern about this concept. It was clearly elaborated by Gross fifty years ago and checks with the known facts concerning the duration of life in patients with cancer of the breast who have not been operated

on or treated, in whom the extremes of survival range from the fulminating, so-called inflammatory types, with death occurring sometimes within eight or ten weeks after the first appearance of the tumor, to those of the chronic, slow-growing tumors with death occurring sometimes as late as twenty-five or more years after the malignant growth was recognized.

The desirability of being able to recognize the relative malignancy of different tumors has long been acknowledged. A number of attempts have been made to grade the malignancy of different tumors of the breast by distinguishing their histologic characteristics, such as adenocarcinoma and medullary, scirrhous, colloid, etc., tumors; with the exception of adenocarcinoma and colloid tumors, these divisions have proved of little value in prognosis. More recently, Greenough has shown that by taking into consideration a number of factors observable in the histologic picture, it is possible to arrive at a fairly accurate estimate of the relative malignancy of tumors of the breast.

Recognizing fully the desirability of developing laboratory methods for estimating the prognosis of cancer of the breast, I nevertheless wish to call attention to the fact that in almost every patient with cancer of the breast the surgeon has at his own command readily available clinical methods by which he can estimate at least some of the factors of malignancy as shown by the behavior of the growth up to the time of operation. A study of the individual histories of the cases here summarized and of other cases reported in the literature would seem to indicate that in the present state of knowledge the actual malignancy of the individual case can probably as yet be most accurately estimated by the careful observation of the extent of the growth and metastases at the time of operation—and the estimation of the rapidity of growth and metastases in terms of the period which has elapsed between the first discovery of the tumor and the time of operation.

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MAJOR AMPUTATIONS

ANALYSIS AND STUDY OF END-RESULTS IN FOUR HUNDRED AND TWENTY CASES

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BOSTON

The following observations are based on an analysis and study of the end-result of 420 major amputations at the Massachusetts General Hospital. The group includes all the major amputations which were performed at this hospital from 1916 to 1926.

An idea of the frequency of amputation may be obtained by comparison of the total number of admissions to the hospital to the total number of operations performed during the same period. There were 65,476 admissions to the hospital, including both medical and surgical cases; the cases in which amputation was performed, therefore, represented 0.64 per cent of the total admissions. During the same period, 39,746 operations were performed, the amputations constituting a little more than 1 per cent of all the operations. Of the 420 cases in the group, primary amputation was performed in 360 and secondary operations or reamputations in sixty.

Table 1 shows the causes of amputation in this group of cases. It is interesting to note that amputations were not performed because of thermal or chemical injury. New England winters are fairly severe, but gangrene resulting from frostbite apparently is decreasing, probably due to more intelligent care of the feet and better methods of transportation.

Following amputation and prior to discharge from the hospital, forty-nine deaths occurred, an operative mortality of 11.6 per cent. In addition, there were ten cases of complete traumatic amputation in which the patient died soon after admission without operation being performed. The inclusion of these cases in the group would give a total hospital mortality of fifty-nine, or 16.3 per cent.

The causes of death are shown in table 2.

Table 3 shows the various postoperative complications which occurred in 420 cases of amputation.

In studying this table, it should be remembered that many of the conditions listed as complications merely represent the continuance of the original condition which necessitated amputation.

The distribution of the different amputations in respect to anatomic location is shown in table 4.

TABLE 1.—*Cause of Amputation*

Percentage	Cause	Total	Primary Cases	Thigh	Lower Leg	Upper Arm	Forearm
26.9	Trauma	113	104	26	37	23	27
10.0	Sepsis	42	35	21	19	0	2
9.5	Endarteritis thrombo-angeitis Reynard's	40	30	19	18	0	3
9.5	Painful amputation stump	40	21	13	27	0	0
8.8	Tuberculosis	37	37	9	19	3	6
8.5	Diabetes (gangrene)	36	28	21	15	0	0
8.5	Arteriosclerosis (gangrene)	36	35	29	7	0	0
7.1	Sarcoma	30	28	21	3	6	0
2.6	Carcinoma	11	11	3	4	1	3
2.3	Thrombosis and embolism	10	9	7	2	1	0
1.9	Gas bacillus infection	8	8	4	1	1	2
0.9	Ununited fracture	4	4	3	1	0	0
0.7	Ruptured brachial plexus	3	3	0	0	3	0
0.7	Spina bifida	3	1	0	3	0	0
0.4	Charcot joint	2	1	1	1	0	0
0.2	Foot deformity (contracture)	1	1	0	1	0	0
0.2	Trophic ulcer	1	1	0	1	0	0
0.2	Tetanus	1	1	1	0	0	0
0.2	Pressure of pelvic tumor	1	1	1	0	0	0
0.2	Gangrene after ligation for popliteal aneurysm	1	1	0	1	0	0
		420	360	179	160	38	43

TABLE 2.—*Postoperative Mortality in 360 Primary Amputations*

Cause of Death	Number	Percentage
Shock, traumatic or postoperative *	9	2.1
Septicemia	10	2.3
Bronchopneumonia	8	1.9
Diabetes	5	1.3
Gas bacillus infection	3	0.8
Cause undetermined	3	0.8
Pulmonary embolism	2	0.5
Cardiac decompensation	2	0.5
Tetanus	1	0.2
Pulmonary tuberculosis	1	0.2
Uremia	1	0.2
Polycythemia (multiple infarction)	1	0.2
Pneumothorax	1	0.2
Cerebral thrombosis	1	0.2
Lobar pneumonia	1	0.2
	49	11.6

* Ten patients with complete traumatic amputation died soon after admission without any operation being performed, but are not included in this tabulation.

TABLE 3.—*Four Hundred and Twenty Amputations: Postoperative Complications*

Total	Percentage	Complications	Thigh	Lower Leg	Upper Arm	Forearm
77	20.8	Wound infection (pyogenic)	35	31	4	4
17	4.1	Extensive slough of flap	8	8	0	1
14	3.3	Postoperative shock	8	3	2	1
12	2.8	Septicemia	8	2	0	2
11	2.6	Gas bacillus infection (B. Aerogenes capsulatus)	5	4	0	2
10	2.4	Bronchopneumonia	7	2	0	1
8	1.9	Extending gangrene	2	6	0	0
3	0.7	Diabetic coma	1	1	0	1
2	0.4	Pulmonary embolism	2	0	0	0
2	0.4	Postoperative hemorrhage	2	0	0	0
2	0.4	Osteomyelitis	0	1	1	0
1	0.2	Cerebral thrombosis	1	0	0	0
1	0.2	Tetanus	0	1	0	0
1	0.2	Auricular fibrillation	1	0	0	0
1	0.2	Cardiac decompensation	1	0	0	0
1	0.2	Pneumothorax	0	1	0	0
1	0.2	Diabetic acidosis	1	0	0	0
1	0.2	Phlebitis	0	0	0	1
1	0.2	Uremia	1	0	0	0
1	0.2	Delirium	1	0	0	0
167	41.6		84	63	7	13

It will be noted that amputations of the upper extremity constitute only 21 per cent of the entire group, in contrast to 79 per cent for the lower extremity. This small figure reflects not only the more conservative attitude of the surgeon in regard to amputation of the upper extremity, but also the lesser incidence of grave pathologic processes here in comparison with the lower limb.

Table 5 shows the number of patients who had more than one limb amputated at one admission. Practically all of these cases were of traumatic etiology.

The duration of hospitalization may be taken as a fair index of the length of time required for convalescence from operations. This does

TABLE 4.—*Types of Amputation (420 Cases)*

Type	Number	Percentage
Amputation thigh	155	37
Amputation lower leg	152	36
Amputation forearm	43	12
Amputation upper arm	30	7
Gritti-Stokes amputation	13	3
Disarticulation hip	9	2
Disarticulation shoulder	8	2
Syme amputation	6	1.4
Amputation through tarsus	3	0.7
Disarticulation knee	1	0.2
	420	

TABLE 5.—*Multiple Amputations at One Admission*

Limbs Amputated	Number of Cases
Both thighs	5
Both lower legs	3
Upper arm and thigh	1
Forearm and lower leg	1
Both lower legs and one forearm	1
	11

not refer to complete healing of the wound, as many of the patients required surgical dressings after leaving the hospital. It implies, however, that the wound was small enough to be safely handled in the outpatient department. Table 6 shows the period of hospitalization for the principal amputation groups, including both open and closed wounds.

The number of open and closed amputations in this group of cases, also the frequency of the use of drainage materials are shown in table 7.

It is always a matter of judgment whether an amputation wound should be closed or left open, and in the former case, whether or not drains should be inserted. In this group of cases, the open type of amputation has usually been employed when the amputation was performed for acute infection. When the infection was chronic or of a low grade of virulence, or situated at a considerable distance from the level of amputation, the wound has sometimes been closed loosely, drains

being inserted. The open type of amputation has been employed also in many of the traumatic amputations. Here is has been the policy to divide the limb at the level of the wound or of the fracture if one existed, to excise all soiled and devitalized tissue, saving as much healthy skin as possible to aid in the latter closure at a later period and to leave the wound open.

In all cases of open amputations, extension has been applied to the skin soon after the operation to prevent retraction of the skin and soft parts. Most of these wounds have been left to heal by granulation

TABLE 6.—*Period of Hospitalization*

	Cases	Longest Stay, Days	Shortest Stay, Days	Average Stay, Days
Amputations of the thigh	174	180	10	41
Amputations of the lower leg	161	198	9	36
Amputations of the upper arm	37	71	7	26
Amputations of the forearm	42	66	9	23

TABLE 7.—*Frequency of Open Amputation, Closed Amputation, and Use of Drainage*

	Percentage	Total	Thigh	Lower Leg	Upper Arm	Forearm
Open amputations	12.4	36	16	13	3	5
Closed amputations	87.6	254	103	101	25	25
a. With drainage	72	183	67	70	23	23
b. Without drainage	28	71	36	31	2	2

TABLE 8.—*Wound Healing in Thirty-Six Open Amputations*

	Percentage	Total	Thigh	Lower Leg	Upper Arm	Forearm
Healed by granulation	58.3	21	9	5	3	4
Closed by secondary suture	11.1	4	2	2	0	0
Required skin grafting	22	8	4	3	0	1
Not healed at discharge	8.3	3	1	2	0	0

(table 8). Some have been treated by the Carrel-Dakin method of wound sterilization, and of these a few have been closed successfully by secondary suture. In some of the cases, healing has been hastened by grafting of skin.

In cases of open amputation, the patients have uniformly made favorable progress, and acute septic complications have been rare. On the other hand, secondary plastic operations or reamputations have been required later in most of these cases to secure suitable stumps for limb fitting.

In primarily clean cases, the amputation has been of the closed type. Drains have been inserted in 183 of 254 such cases, or 72 per cent; frank

infection of the wound occurred in forty-nine, or 19 per cent. This is a high incidence and can probably be explained on the ground of reluctance on the part of some surgeons to use the open type of amputation in cases of infection, and the attempted closure of wounds which would have done better if left open.

We have a strong feeling that drains often are needlessly inserted in clean amputation wounds. If bleeding is carefully arrested, there is no more reason for the use of drains than in clean operative wounds elsewhere. We are convinced that many of the persistent sinuses which are prevalent in amputation wounds are the direct result of infection which has gained entrance along the drain tract. This might not occur if the drains were removed as a routine at the end of from twenty-four to forty-eight hours; unfortunately, they are usually allowed to remain

TABLE 9.—*Wound Healing in 254 Closed Amputations*

	Percentage of Each	Thigh	Lower Leg	Upper Arm	Forearm	Total
Healed by first intention						
With drainage	37.1	30	12	16	10	68
Without drainage	42.2	18	11	1	0	30
Healed by granulation						
With drainage	32.2	22	20	4	7	50
Without drainage	32.5	8	14	0	1	23
Frank wound infection						
With drainage	20.2	14	16	3	4	37
Without drainage	16.9	7	3	1	1	12
Not healed at discharge						
With drainage	10.3	1	16	0	2	19
Without drainage	8.5	3	3	0	0	6
Secondary closures		3	6	2	0	11
Skin grafting required		0	4	0	2	6

much longer. When infection is feared, it is a better policy to leave the stamp open than to close with drainage. Infection of the wound in a closed stump delays convalescence enormously, and almost invariably necessitates reamputation later. There is a sacrifice of stump length at the time of the original amputation in order that the flaps may be formed from clean tissues, and the reamputation entails still further loss. The open amputation, on the other hand, can be performed at the lowest possible level, and although a secondary operation is usually required, this need not be a formal reamputation. It conserves function, and the results are so good that there would not seem to be any justification for the policy of closure with drainage. The rule ought to be either to close tight or to leave wide open in all but exceptional cases.

Table 9 shows the wound complications in the cases of closed amputations. It will be noted that the figures are slightly but almost uniformly better in the cases in which drainage is not used.

END-RESULTS

A follow-up study has been made of the 360 cases of primary amputation included in this group. End-results have been ascertained in 253 cases, or 70 per cent, of the total. As these amputations were performed from 1916 to 1925, inclusive, it will be seen that none of the results was obtained less than one year postoperatively, and that the majority are of much longer duration (table 10).

The causes of death of those who have died since leaving the hospital are shown in table 11.

Data have been sought with regard to three main points, as follows:

1. Functional results in relation to amputations at different levels.

2. Surgical results as indicated by the number of reamputations and secondary operations.

3. Disease results with regard to the cure of the condition which necessitated amputation.

TABLE 10.—*End-Result Tabulation (360 Primary Amputations)*

	Number		Percentage
Postoperative deaths in hospital	49	or	13.6
Known deaths since leaving hospital	56	or	15.5
Alive and end results known	148	or	41
Total number of end results	253	or	70.2
Not located	107	or	29.8
	360		100
Reamputation required in	52	or	14.4

The cases have been analyzed from these three points of view, and the results will be presented under these three headings.

FUNCTIONAL RESULTS

The end-results with reference to present function have been grouped according to the level of amputation.

Disarticulation of the Hip.—There were nine cases of disarticulation of the hip with a postoperative mortality of two or 22 per cent. Notes on the functional end-result have been obtained in three of the remaining seven cases; the other patients have either died or have not been located.

Two of the patients found were adults and the other was a boy, aged 11. In the former, the cause of amputation in one case was old tuberculous disease of the hip joint with secondary pyogenic infection, in the other, a high traumatic amputation leaving a stump which was covered with a broad, thin, sensitive scar and was too short to actuate an artificial leg. Secondary disarticulation of the hip was performed to improve the functional result, and it is interesting to note that this patient was the only one of the three to make use of an artificial limb. The third case was that

of a boy who had an osteogenic sarcoma of the femur. Disarticulation of the hip was performed and he is alive and well at the end of two years without any sign of recurrence or metastasis.

Only one of these three patients uses an artificial leg. He is a teacher in an agricultural college, and has to walk and be on his feet a great deal. He walks with little apparent limp and carries his heavy prosthesis without difficulty. The other two patients rely entirely on crutches. The boy has not been fitted with a leg because he is growing, and the parents are unable to bear the expense of the frequent refitting which would be necessary. He has become so agile on crutches that he probably will never attempt to use a limb. The third patient had not been able to use his diseased leg for twenty years previous to amputation. He had become entirely accustomed to crutches and decided that a prosthesis would be a handicap rather than a help.

TABLE 11.—*Causes of Death After Leaving Hospital*

Tuberculosis	11	Septicemia	1
Cerebral hemorrhage	9	Appendicitis	1
Carcinoma	5	Uremia	1
Sarcoma	8	Acute nephritis	1
Diabetes	3	Chronic nephritis	1
Myocarditis	3	Burns	1
Cardiac decompensation	1	Suicide	1
Arteriosclerosis	2	Not stated	4
Angina pectoris	1		54

All three of these patients have continued at the same occupation they followed before disarticulation was performed. One works as assembly man in a factory manufacturing bankbooks, one is a teacher, and the third is a school boy. Neither of the adults has sustained any economic loss as the result of the loss of the leg, and the boy will be trained for some work within his physical capacity.

Amputation of Thigh.—Amputation of the thigh was performed in 155 cases, or in 37 per cent of the entire group of patients. There were twenty-three postoperative deaths, or a mortality of 14.8 per cent. Of those surviving, sixty-seven are living and have been heard from. Forty-five, or 67 per cent, are using artificial limbs; eighteen of these have been personally examined, the length of the stump measured in relation to the length of the normal femur, and accurate notes made of the functional result (table 12). It will be noted that the percentage of poor functional results was largest in amputations in the upper third (three of five); next largest in amputations in the middle third (three of eight), while in the lower third, poor results were not observed.

In most cases of amputation of the thigh in which an artificial limb was not worn, it was because of disease or debility such as cardiac weak-

ness, diabetes, mental deficiency or senility. In three cases it was because of lack of funds.

The prosthetic history was noted in twenty-eight cases. This is shown in table 13. The best results were obtained in those cases in which a temporary appliance had been fitted. This was of the peg leg type, usually constructed from the lower half of a crutch with plaster of paris socket. Such an appliance had been used in ten of the twenty-eight cases, being fitted on the average 1.6 months after the operation. Because of the simplicity and light weight of such an appliance, the patient is able to use it even when the stump is still sensitive. It

TABLE 12.—*Amputations of the Thigh: Functional Result in Relation to Length of the Stump*

Length of Stump	Good	Fair	Poor	Total
Upper third	1	1	3	5
Middle third	5	0	3	8
Lower third	2	3	0	5
	8	4	6	18

TABLE 13.—*Prosthetic Results After Amputation of the Thigh*

Using artificial leg		24
No difficulties experienced	21	
Fit of limb unsatisfactory	3	
Not using artificial leg		4
Patient too weak	1	
Limb too heavy	3	
Total		28
Fitted with provisional appliance		10
Average time from operation to receiving temporary appliance		1.6 months
Average time from operation to receiving permanent leg		
When provisional leg had not been used (19 cases)		13.3 months
When provisional leg had been used (9 cases)		5.5 months
Average time saved		7.8 months

improves the circulation in the stump, hastens shrinkage, strengthens the muscles and restores the normal mobility of the joints far better than any other agents.

The economic side always looms large in the cases of amputation of the thigh. Notes as to occupation were made on thirty-two patients (table 14), seventeen of whom are working and are wholly or largely independent, while fifteen have no occupation and are entirely dependent. Nine of these are men over 64 years of age with various forms of senile debility. Most of the others are suffering from some form of disease. Of the seventeen who are employed, six are working at the same occupations as prior to amputation and have not been affected economically; the rest have had to change their occupations and to find tasks fitted to their disability.

Some excellent results were noted. Three are able to walk a distance of from two to three miles, and several work at jobs which necessitate standing all day. The best results were seen in patients with stumps of good length, in which healing had occurred by first intention. Two of the best results noted in patients on whom the Gritti-Stokes amputation had been performed and who had been fitted with full end-bearing legs. One of these patients was working as a machinist, the other as a labor gang foreman; there was scarcely any disability in either case.

TABLE 14.—*Occupations of Persons on Whom Amputations of the Thigh Was Performed*

Number	Present Occupation	Former Occupation
Working—17 Patients, 53 per Cent		
1	Janitor	Freight brakeman
1	Shoe factory, machine operator	Same
1	Shoe factory, stitcher	Housework
1	Factory employee	Tailor
2	Odd jobs	Coal helper, lunch counter
1	Auto mechanic	Same
3	Student	Same
1	Clerk	Same
1	Cobbler	Factory worker
1	Pedler	Laborer
1	Dressmaking	Same
1	Draftsman	Student
1	Machinist	Same
1	Labor foreman	Laborer
Not Working—15 Patients, 47 per Cent		
	Reason for Not Working	**Former Occupation**
9	Senility in various forms	Farm laborer 2 Laborer 1 Blacksmith 1 Barber 1 Card shop 1 Cook 1 None 2
1	Poor circulation in legs (endarteritis)	None
1	Osteomyelitis, multiple foci	School boy
1	Painful stump	Housework
1	Receiving industrial compensation	Laborer
1	Cannot walk with leg	Painter
1	Diabetes	Tailor

Amputations of the Lower Leg.—There were 152 amputations of the lower leg or 36 per cent of the 420 cases. There were ten deaths, a postoperative mortality of 6.5 per cent. Fifty-two of the surviving patients are still alive and have been heard from; the rest have either died or not been located. Forty-four, or 85 per cent, are wearing artificial legs, a much better showing than in amputations of the thigh where the proportion was only 65 per cent. It was found that no patient who was well enough to walk went without prosthesis.

The functional results were usually better than in cases of amputation of the thigh. Several of the patients said that they could walk any distance, and twenty-eight of thirty-three on whom occupational notes were made were working, fifteen at the same job as before amputation. Several of the occupations involved heavy work, two patients being

laborers. The list of occupations is shown in table 15. Of the seven patients not working, all but two had definite disabilities.

Twenty-four of thirty patients using artificial legs reported good function and no disabilities (table 16). Six patients were having trouble either with their stumps or with their legs. Nine patients have had to have their appliances changed, some of them twice. All this indicates that it is much more difficult to secure a satisfactory fitting leg in the case of amputations of the lower leg than in amputations of the thigh. Stump troubles are common, especially in summer. Chafing over the head of the fibula occurs frequently, and in many such cases the patient would

TABLE 15.—*Occupations of Persons on Whom Amputations of the Lower Leg Had Been Performed*

Number	Present Occupation	Former Occupation
	Working—26 Patients, 79 per Cent	
5	Housework	Same
2	Laborer	Same
3	Switchman	Brakeman
1	Clerk	Traveling salesman
1	Elevator man	Laborer
2	Janitor	Truck driver, same
1	Child's nurse	Laundress
1	Watchman	Same
1	Student	Same
2	Cigar maker	Same
1	Presser	Tailor
1	Shoe treer	Same
1	Hoisting engineer	Same
1	Dressmaking	Same
1	Insurance broker	Traveling salesman
1	Store clerk	Farmer
1	Tailor	Same
	Not Working—7 Patients, 21 per Cent	
	Reason for Not Working	**Previous Occupation**
3	Various forms of senile debility	Carpenter, salesman, railway inspector
2	Painful stump	Brakeman, metal junk dealer
2	No reason stated	Mill operator, labor foreman

be relieved by complete excision of the fibula. On the other hand, when there is a good stump and a well fitting leg, the disability is almost negligible.

The results obtained by the use of temporary appliances are not so striking in amputations made below the knee as in the case of amputations of the thigh. This is because a more complicated appliance is used, one that has to be obtained outside the hospital. There is often considerable delay in fitting it, the average time being 3.5 months as against 1.6 months in the amputations of the thigh. There is no reason why these patients should not be fitted with temporary appliances as early as those on whom amputations of the thigh have been performed; if this were done, we are confident that the same saving of time would result in the period between operation and the fitting of the permanent limb as in the former group of cases.

Syme Amputation.—The value of the Syme amputation in properly selected cases is demonstrated by a study of the end-results. There were six of these cases in which death did not occur; all the patients have been traced. The amputation was a failure in one because of improper selection. This patient was a boy, aged 9, who had spastic paraplegia and paralytic equinovarus deformity of both feet and trophic ulcers caused by spina bifida. There were areas of cutaneous anesthesia involving both feet and lower legs, also involvement of both vesical and rectal sphincters. After a long period of unsuccessful orthopedic treatment, bilateral Syme amputations were performed. The boy later developed trophic ulcers on the ends of the stumps when weight bearing was begun. Amputation of the mid leg was performed on one side and two years later the same procedure became necessary on the other side. The boy

TABLE 16.—*Prosthetic History: Amputation of the Lower Leg*

Using artificial leg		30
Good function, no difficulties experienced	24	
Have used artificial leg but complain of difficulties as follows:		
Sore on stump	1	
End of stump sensitive	1	
Leg too heavy for stump	1	
Chafes	1	
Fit of leg unsatisfactory	2	
Have had to change leg as follows		9
Socket changed twice	2	
Have had to buy new leg	6	
Leg replaced twice	1	
Fitted with provisional appliance		13
Average time from operation to receiving temporary appliance		3.5 months
Average time from operation to receiving permanent leg		
When provisional appliance had not been used		9.5 months
When provisional appliance had been used		8.2 months
Average time saved		1.3 months

died of uremia. This case illustrates the necessity of normal innervation of the skin at the end of the Syme stump if a successful result is to be obtained. The virtue of the Syme amputation lies wholly in the complete end weight bearing ability of the stump. If this result is not obtained, then amputation of the mid leg is preferable.

In the remaining five cases Syme amputation was performed because of the following lesions: tarsal tuberculosis, two cases; unsatisfactory Chopart amputation, one; painful and contracted foot resulting from burns, one, and hemiplegia with incorrectible deformity of foot, one.

The results in all cases were successful as regards complete end-weight bearing ability. All of the patients were able to walk across the room on the bare stump. Four were fitted with end-weight bearing appliances; the fifth obtained his artificial limb without medical guidance, and was given an improper type of leg which does not utilize end-bearing. One patient required a secondary operation because of a painful exostosis at the end of the fibula.

The functional results are good in four cases and fair in one. The latter is a case of hemiplegia, and although the former deformity of the foot has been eliminated, considerable disability remains due to spasticity. All are working, being employed as shown in table 17. It will be noted that three are doing the same heavy type of work as before amputation.

The prosthetic result is good when a proper type of appliance is fitted. The ankle is large and bulky, however, and the cosmetic result in the case of a woman would not be satisfactory. For this reason, the operation has been performed only on men.

Double Amputations of the Lower Extremities.—Notes on the end-results have been obtained in ten cases of double amputations of the lower limbs, and are shown in tables 18 and 19. As would be expected, the disability resulting from double amputation of the thigh is total. In four such

TABLE 17.—*Occupations: Syme Amputation*

Number of Cases	Present Occupation	Previous Occupation
1	Longshoreman	Same
1	Farm laborer	Same
1	Pedler	Same
1	Switchman	Trainman
1	Messenger	Watchman

TABLE 18.—*Results in Double Amputations of the Lower Extremities*

	Number of Cases	Using Appliances	Working	Not Working	Disability Percentage
Amputation of both thighs.....	4	1 occasionally	0	4	100
Amputation of thigh and lower leg	2	1	2	0	75
Amputation of both lower legs.....	4	3	2	2	50 to 75

cases the patients are wholly dependent and live a wheel chair life. One has been fitted with short peg legs, and with these and the aid of canes he is able to get about a little. Double amputations of the thigh and lower leg yield considerably better results. Two cases of this type were followed. One patient gets about fairly well, the other is not able to walk. A great deal depends on whether the patient is in good general health and possesses the necessary initiative and determination. In bilateral amputations of the lower part of the legs, good functional results are obtained, provided the stumps are sound and the general health and strength good. One of our four patients is working as a laborer, although doubtless the work is made as light as possible for him. Three are using appliances with satisfactory function. The fourth is in poor health and cannot use prostheses.

Amputations of the Upper Extremity.—Notes on end-results were obtained in thirty-four cases of amputation of the upper extremity, of which nineteen were amputations of the forearm and fifteen amputations

of the upper arm. Death could not be ascribed to the amputation in any case, although several patients died as a result of the original disease process.

Only two of the fifteen patients who had the upper arm amputed are using appliances. One of these is employed as a clerk in a shipping house and derives some practical benefit from his prosthesis. The other does not have an occupation and wears his appliance presumably for cosmetic reasons. Only four of the nineteen patients who had the forearm amputated, use appliances. Two of these use prostheses of the split hook type, but only part of the time; the rest of the time they use nothing. The other two wear artificial hands. The occupations of these four men are: contractor, one; elevator operator, two, and sales clerk in store, one.

Apparently the length of stump made little difference as far as the functional results was concerned. The uninjured arm was depended on almost altogether and made to do the work of two. In the amputations

TABLE 19.—*Occupations in Double Amputations of Lower Extremities*

Level	Number	Present Occupation	Former Occupation	Reason for Not Working
Amputation of both thighs.....	4	None	None	Total disability
Amputation of thigh and lower leg..	1	Bead making at home	Laborer	No prosthesis does not walk
Amputation of thigh and lower leg..	1	Spanish correspondent	Salesman	
Amputation of both lower legs.....	1	None	Laborer	Endarteritis
Amputation of both lower legs.....	1	None	None	Senile debility
Amputation of both lower legs.....	1	Agency work	Car inspector	
Amputation of both lower legs.....	1	Laborer	Same	
Total	10			

of the forearm the stump was used considerably to aid the normal hand in the performance of certain tasks. In amputations of the upper arm the stump was used little.

In respect to occupation, all either did not have an occupation or did work, which did not require the use of two hands. The class of work, however, done by the patients whose forearm had been amputated was in general a little more difficult than that done by those whose upper arm had been amputated. The occupations, when known, are shown in table 20.

From the little use that was made of appliances in this group of thirty-four cases, it would seem evident that small weight should be given to prosthetic considerations in determining the point at which an amputation of the upper extremity should be performed. Cure of the original disease process and obtaining a painless, nonsensitive stump are the chief goals to be sought.

Prosthetic Summary.—In amputations of the thigh most patients who were able wore artificial legs. When these were not used, it was gen-

erally because of debility due to old age, to disease such as diabetes, or cardiac weakness.

In amputations of the lower leg no patients who were well enough to walk did not use prostheses.

Scarcely any of those whose upper arm had been amputated used appliances; when these were used, it was only for cosmetic reasons.

TABLE 20.—*Occupations of Persons on Whom Amputations of Upper Extremity Have Been Performed (19 Cases)*

Region of Amputation	Number	Present Work	Previous Work	Remarks
Disarticulation of the shoulder	1	Labor foreman	Laborer	Earns more than formerly
	2	None	None	Feebleminded
	3	Office work	Same	
Amputation of the upper arm	1	Clerk	Same	
	2	Watchman	Laborer	
	3	Housework	Same	
	4	None	None	In state asylum
	5	Construction work	Same	
	6	Storekeeper	Same	
	7	Order clerk	Schoolboy	
	8	Railroad watchman	Brakeman	
Amputation of the forearm	1	Salesman	Printer	
	2	None	Laborer	Old man of 63
	3	Fireman's helper	Factory work	
	4	None	Laborer	Old man of 70
	5	General work	Shipper	
	6	Delivery clerk	Laborer	Earns more money
	7	School	School	
	8	Contractor	Same	Does everything

TABLE 21.—*Prosthetic Results*

	Amputations of the				
	Thigh	Lower Leg	Upper Arm	Forearm	Total
Patients alive and reporting	67	52	15	19	153
Wearing prostheses	45	44	2	4	95
Percentage using prostheses	67	85	13	21	62

In cases of amputations of the forearm, appliances were used a little more often than in cases of amputations of the upper arm and the appliances appeared to be of some practical benefit.

Temporary prostheses were fitted in twenty-two cases and appeared to be of definite value in shortening the period between operation and the fitting of the permanent limb. The functional results were also better.

In sixty-two cases the average time from operation until the delivery of the permanent limb was 9.3 months. This period is needlessly long. The best method of shortening the time interval is by the fitting of temporary prostheses. These were employed in twenty-two cases, and the average time until the permanent limb was fitted was seven months.

REAMPUTATIONS AND SECONDARY OPERATIONS

Of the 420 cases of amputation included in our study, sixty-nine, or 16.4 per cent, were classified as reamputations. This term is often used inexactly to denote any operation on an amputation stump irrespective of its nature, and it is probable that some cases were included among our cases of reamputation in which only local operations had been performed, such as sequestrectomy, excision of neuroma or resection of painful scar. It was sometimes difficult to determine from the records exactly what had been done.

The causes for which reamputation was performed are shown in table 22. Study of this list shows that many of the conditions were unavoidable and that they were often to be attributed to the circumstances under which the original amputation had been performed. Such were some of the cases of osteomyelitis, adherent scar and unsatisfactory

TABLE 22.—*Causes of Reamputation (69 Cases)*

Causes	Thigh	Lower Leg
Stump unsuitable for prosthesis:		
Osteomyelitis with sinus	2	2
Ulcer on end of stump	4	17
Neuroma end of stump	1	0
Painful (not described)	3	1
Adherent scar	1	1
Exostoses on stump	1	2
Retracted flaps, bones under skin	1	2
Deformity of foot	0	1
Unsatisfactory, cause not stated	2	3
Extending gangrene:		
Thrombo-angiitis	0	3
Diabetes	0	5
Arteriosclerosis	0	3
Extensive sepsis in wound	3	8
Recurrent sarcoma	1	0
Gas bacillus infection	0	1
Carcinoma	0	1
	19	50

stump covering which resulted from open amputations. The necessity of a secondary operation in such cases does not reflect on the surgeon who performed the primary amputation. It has been a great satisfaction to note that so little trouble was experienced from the development of painful neuromas. The good results here are to be ascribed to the fact that the technic of Huber and Lewis [1] for injection of alcohol was adopted at the Massachusetts General Hospital in 1919, and that it has been used in practically all cases of amputations since that time.

On the other hand, many of the reamputations were the result of mistakes in judgment or technic and might have been prevented. Among these were several amputations in the lower third of the lower leg. Such amputations give trouble almost invariably, the end of the stump lacking proper blood supply and tending to become cold, cyanotic and sensitive, and later, to ulcerate. In several other cases of amputation of the lower

1. Lewis and Huber: Amputation Neuromas, Arch. Surg. 1:85 (July) 1920.

leg trouble was experienced because the fibula had not been properly shortened. There were also several cases of amputation for sepsis in which closure of the wound had been attempted with the consequence that extensive infection had developed, and reamputation at a higher level had been required. This result might have been prevented if the original amputation had been of the open type.

In sixteen instances, it was necessary by reamputation to convert amputations of the lower leg into thigh stumps. In eleven cases, this was because of failure to arrest a gangrenous process by amputation in the lower leg. Five of these cases were of diabetic origin; three were due to arteriosclerosis and three to thrombo-angiitis. In the remaining five cases, one reamputation was due to extension of sepsis, one was a primary amputation for tuberculosis which developed osteomyelitis of the tibia, and three were amputations for trauma in which reamputation was necessitated by ulceration of the stump in two instances and in the third by the development of gas bacillus infection in the sutured wound. In the latter case, it was necessary to amputate by the open method at midthigh. Experience shows that in diabetic and arteriosclerotic gangrene, it is practically always a mistake to amputate below the knee. The best operation in such cases is the Gritti-Stokes amputation. As a rule, difficulty in healing is not experienced and infinitely better functional results are obtained. In thrombo-angiitis, on the other hand, on account of the younger age of the patients and the bilateral character of the process, it is better to amputate in the lower leg if the chances are fair.

There were two cases of secondary disarticulation of the hip joint following original amputations of the thigh. One of these was of traumatic origin and the amputation was in the upper third, leaving a stump too short for prosthetic purposes. Disarticulation was advised as a means of improving function, and this patient has achieved a satisfactory result with the aid of an appliance. In the other case, amputation was originally performed at midthigh for an enchondroma of the lower end of the femur. After four years, the tumor recurred in the stump, and disarticulation was then performed. The patient later died of metastasis.

There were three deaths among the cases of reamputations. These were cases of extending gangrene in elderly patients, two of diabetic and one of arteriosclerotic origin. The mistake was made of performing the primary amputation below the knee. The gangrene continued to spread, and it was then necessary to reamputate at midthigh. The deaths were due to senile complications. More than one reamputation was required in two cases. Additional stump operations were required in seventeen, but these were of localized character, and did not involve sacrifice of the length of the stump.

Most of the results from reamputation were satisfactory. Considerable difficulty was experienced with the wounds, only twenty-eight, or 42 per cent, healing by first intention (table 23). This was the result of the low grade sepsis present in many of the cases. Two reamputations were of the open or flapless type, one due to gas bacillus infection, and the other to pyogenic infection.

In twenty of the cases in which reamputation was required, the primary amputation had been performed elsewhere; in the remaining forty-nine cases, both the primary and secondary amputations had been performed at the Massachsetts General Hospital. In addition, it was

TABLE 23.—*Results of Reamputation (69 Cases)*

Open amputations (healed by granulation)		2
Closed amputation wounds		64
Healed per primum	28 or 42.4%	
Healed by granulation	25 or 37.8%	
Not healed at discharge	8 or 12.1%	
Died of extending gangrene (2 diabetic and 1 arteriosclerotic, with senile complications)		3
		69

TABLE 24.—*Distribution of Reamputations with Reference to Primary Amputations*

Primary Amputation Elsewhere		Reamputation Massachusetts General Hospital	
Thigh	Lower Leg	Thigh	Lower Leg
0	20	2	18
Primary Amputation Massachusetts General Hospital		**Reamputation Massachusetts General Hospital**	
Thigh	Lower Leg	Thigh	Lower Leg
12	27	23	16
Local operations	8		9
Primary Amputation Massachusetts General Hospital		**Reamputation Elsewhere**	
Thigh	Lower Leg	Thigh	Lower Leg
3	1	3	1

found by inquiry concerning the cases which had been followed up that four patients on whom primary amputation had been performed at the the Massachusetts General Hospital had later had secondary operations performed elsewhere. Therefore, of the group of 360 primary amputations, later reamputation was required in fifty-three or 14 per cent.

END-RESULTS WITH REFERENCE TO DISEASE GROUPS

Amputations Due to Trauma.—In the group of 360 primary amputations, 113, or 26.9 per cent, resulted from trauma, more than twice the number due to any other cause. This represents only the cases in which surgical amputations were performed. In addition, there were ten patients with complete traumatic amputation who died shortly after arriving at the hospital. These were not included in the group because

surgical operation was not performed. The ages of the patients varied from 4 to 70 years; the average age for the entire group was 36 years. The majority of the patients were in the active, wage-earning period, and exposed to trauma by reason of their occupations. On the two extremes were the children and elderly persons who in the main received their injuries in accidents in which they were run over.

Type of Injury: All of the patients requiring amputation because of trauma had received severe injury, usually of a direct crushing character. The majority had sustained partial amputations, the limbs being so extensively damaged that they could not be saved. Complete traumatic severance of the limb occurred in forty-four cases. In six cases amputation was necessitated by vascular damage with the development of gangrene a few days after injury. Many of the patients had complicating injuries, often multiple, of other parts of the body such as thoracic or visceral injuries, fractures of the skull or pelvis, or bones of the extremities.

Shock: Surgical shock was present in most of the cases. In thirty-three cases, or 29.1 per cent, it was noted as especially severe. Such patients were kept on the heated shock table with the body tilted head downward until their condition improved. They were given large doses of morphine and received subcutaneous and intravenous infusions of saline. In the postwar period blood transfusion was employed in practically all cases as soon as donors could be obtained. This proved a potent life saving measure, and without question, is the most effective method of treating shock. Amputation of the injured limb was not performed until the patient had rallied from his state of shock, with the exception of a few cases in which the limb was attached only by a few shreds of tissue which could be divided without the necessity of an anesthesia and without moving the patient. In the few instances in which this rule was not followed, the patients died. The patient's condition was followed by frequent blood pressure readings. A falling systolic pressure or an initial pressure under 90 mm. mercury is an indication for blood transfusion. A rising pressure is favorable and when it reaches 100 to 110 mm. of mercury, it is usually safe to perform a quick amputation.

Hemorrhage: Many of the patients had sustained severe hemorrhage, often arriving with a tourniquet in place. When it was necessary to use a tourniquet over a considerable time, the practice of releasing the pressure for a period of five minutes every hour was always followed. Whenever possible, the bleeding vessel was clamped off and the tourniquet removed, since pressure by a tourniquet may of itself occasion shock. In many of the complete traumatic amputations, the contusion of the tissues had sealed the vessels so that scarcely any hemorrhage occurred.

It was often difficult, except on the basis of the history, to differentiate between pure surgical shock and shock due to hemorrhage.

Mortality: There were eleven deaths in the group of 113 traumatic amputations, a mortality rate of 9.66 per cent. Five of the patients who died had had amputations of more than one limb. All of these were cases of extreme trauma, and if they are subtracted from the rest, it leaves a mortality rate of 5.3 per cent which is surely low for this type of injury, and evidence that the cases were well treated.

This does not include ten patients who died almost immediately after admission to the hospital. The injuries responsible for the rapidly fatal termination in these particular cases are listed as follows:

1. Complete traumatic amputation of the upper arm and the lower leg; profuse hemorrhage. The patient died in shock soon after admission.

2. Complete traumatic amputation of the thigh; profuse hemorrhage. The patient died in shock soon after admission.

3. Complete traumatic amputation of the left upper arm; fracture of the left femur; fractured pelvis and perineal lacerations. The patient died in shock ten hours after admission.

4. Crush with partial amputation of the right thigh, right forearm; evulsion of scrotum. The patient died in shock two hours after admission.

5. Complete traumatic amputation of the left upper arm; open dislocation at knee; compound fracture of the right tibia. The patient died in shock soon after admission.

6. Complete traumatic amputation of both feet; fractured skull?; ruptured viscus. The patient died soon after admission.

7. Complete traumatic amputation of the right lower leg; multiple fractures; contusions, and lacerations. The patient died soon after admission.

8. Complete traumatic amputation of the left leg at thigh and left arm at shoulder; right foot crushed. The patient died in shock soon after admission.

9. Partial traumatic amputation of the left thigh; fractured skull. The patient died in shock four hours after admission.

10. Complete traumatic amputation of both thighs; fractured skull. The patient died ten minutes after entry.

Distribution: The distribution of the traumatic amputations is shown in table 25. It is to be noted that in the entire amputation group there were only eighty-one amputations of the upper extremity, comprising approximately 20 per cent; of these, trauma was responsible for fifty, or 61.7 per cent. Table 25 shows a comparatively even distribution for the four limb segments. It demonstrates that under modern conditions trauma strikes all parts of the body indiscriminately, in this respect differing from all other pathologic conditions which may cause amputation. The fact that the figure for amputations of the lower leg is slightly larger than for the other parts is to be explained by the greater readiness

of the surgeon when in doubt to sacrifice this part in view of the excellent functional results that may be obtained with the aid of an artificial leg.

Type of Amputation: Figures were obtained as to the type of amputation in ninety-one of the 113 cases. Of these eighteen, or 19.6 per cent, were by the open or flapless method while seventy-three, or 81.4 per cent, were closed by suture. We hold the view that when the injury which necessitates amputation is situated at a useful prosthetic level, better results will be obtained, functional power conserved and postoperative complications rendered less frequent by the use of the open amputation. This should be performed at the level of injury with debridement of soiled and devitalized tissues. Secondary closure may be done when the

TABLE 25.—*Traumatic Amputations, Distribution and Mortality*

	Distribution of Amputations		Mortality	
Region	Number	Percentage	Number of Deaths	Percentage
Forearm	27	23.9	0	0.0
Upper arm	23	20.3	3	2.6
Lower leg	37	32.7	6	5.3
Thigh	26	23.0	2	1.76
Totals	113	99.9	11	9.66

TABLE 26.—*Distribution of Amputations for Sepsis*

Region	Number	Percentage
Forearm	2	4.7
Upper arm	0	0.0
Lower leg	17	40.4
Thigh	22	52.3
Hip	1	2.6

wound has been disinfected or, if this is not possible, a secondary operation may be performed at a later date with excision of scar and plastic closure of the skin. From a study of the results in these cases, we are of the opinion that the open amputation should have been used more frequently than it was.

Amputations Due to Sepsis.—Next to trauma, sepsis was responsible for more amputations than any other cause. This group comprised thirty-five primary amputations and seven reamputations, a total of forty-two cases or 10 per cent, of the entire group. The distribution of the amputations is shown in table 26.

The striking fact about these figures is that the amputations of the lower limb outnumbered those of the upper extremity in the proportion of seventeen to one. There were only two amputations of the arm, both the result of severe septic infections of the hand, and both patients died. The majority of the amputations of the lower limb were due to osteo-

myelitis, either acute or chronic, acute purulent arthritis of the knee or ankle, or to acute infections following traumatic injury. Four followed compound fractures. The amputations were performed for the purpose of saving the life of patients desperately ill or to get rid of a chronically infected part which, from the functional standpoint, was useless and in which there was no outlook for future improvement.

The much greater frequency of the amputations of the lower limb is accounted for partly by the higher incidence of such infections in the leg and by their greater severity here, and partly by the fact that the functional results of amputation of the leg are so much better than those of the arm. In the case of the arm, regardless of how great the crippling, so long as the part is retained, the result will be better than if an amputation is performed. This is not true in the case of the lower extremity, and it is often preferable to sacrifice a portion of a limb than to save it at the expense of prolonged treatment when there is every

TABLE 27.—*End-Results of Amputations for Pyogenic Infection*

Number of cases of primary amputations			35
Died in hospital following amputation		6 or 17%	
Septicemia	4		
Uremia	1		
Shock	1		
Died since leaving hospital		0	
Alive and apparently well		22 or 63%	
Have had reamputations	7 or 20%		
Using artificial appliances	16 or 45%		
Painful stump	1 or 3%		
Incapacitated because of age or physical condition	5 or 14%		
Not located		7 or 20%	

indication that it will at the best be permanently damaged. When dealing with infections of the upper extremity the surgeon does not have the option of sacrificing the limb except when death is likely to occur, whereas in infections of the lower limb the option of amputation is always present, and the surgeon must take into consideration not only the risk to life, but also the future functional value of the limb, the probable duration of the illness, the chances of future trouble and the social and economic status of the patient.

Fourteen, or 38.8 per cent, of the amputations were performed by the open or flapless method, the remainder were closed by suture. The open type of amputation was used in all cases of acute or severe infection. The closed method was used only in subacute or chronic cases, and when the level of amputation was well removed from the seat of the infection.

Results: There were six deaths, four from septicemia following amputation of the thigh, one from uremia following amputation below the knee, and one from shock following disarticulation of the hip, a total mortality rate of 17 per cent. Of the twenty-nine patients with primary

amputations who were discharged from the hospital, twenty-two have been heard from and seven have not been located. Deaths have not occurred so far as we could learn. Of the twenty-two patients examined, or heard from, seven have had secondary operations, four of which were performed because of persistent sinuses. Sixteen are using artificial legs, two are still using temporary appliances, one has a drainage sinus and cannot wear a leg, and the remainder are helpless, either because of age or poor physical condition. The economic status of the patients is the same as for amputations of the same type due to any cause.

Endarteritis, Thrombo-Angiitis, Raynaud's Disease.—This group, consisting of thirty cases and constituting 9.5 per cent of all those studied, includes all cases diagnosed as endarteritis obliterans, thrombo-angiitis obliterans and Raynaud's disease. All the amputations were of the lower limb with the exception of three of the upper extremity, or 7.5 per cent. Of the thirty cases, reamputation was required later in eight. In addition, there were reamputations in ten cases in which the primary amputation had been performed elsewhere. There was a post-operative mortality of four, or 14.7 per cent. The ages of the patients ranged from 27 to 74 years, the average for the group being 44.2 years.

This group of cases is pathetic, the relief obtained from amputation being usually of short duration. The process extends, and sooner or later vascular disturbance develops in the opposite limb, or in the amputation stump, and the patient finally returns for further amputation. One patient has had thirteen amputations beginning with the fingers and ending at the middle of both thighs. Another has had seven amputations, still another five.

Eight of sixteen patients reporting for a study of end-result (table 28) show evidence of progression of the disease either in the stump or the opposite limb, and five have had double amputations. Eleven are using appliances to greater or lesser extent. Eight are able to follow the same or similar occupations. Seven patients are totally disabled, two owing to cardiac disease and three by reason of multiple amputations. One gets about a little as a dealer in junk. Two of the patients with bilateral amputations of the lower legs lead a surprisingly active life and are but little incapacitated.

Slow healing of the wound characterized most of these cases. When drains had been employed, the openings left after the removal of the drains often persisted as sinuses for many months, and in some cases, never healed. It is clear that drains should never be used in cases of this type. The amputations were usually performed by the equal flap method, and sloughing of the flap was of infrequent occurrence. As a rule, a tourniquet was not used. This is important as it allows the surgeon to judge the state of the circulation by the amount of bleeding, and

if this is insufficient, to amputate at a still higher level. There is also a possibility that tourniquet pressure may actually be harmful.

From a knowledge of the after-history of these cases, one is convinced of the futility of amputation as a method of treatment unless it is followed by a prolonged period of after-treatment to improve the circulation of the remaining limb. Limitation of activity and physiotherapy in various forms are the principal therapeutic measures and it would appear necessary to make some provision for the care of these patients with chronic cases in a special institution if improvement in the results is to be obtained.

Tuberculosis.—In the group of 420 amputations, there were thirty-seven, or 8.8 per cent, due to tuberculous infection. All were primary

TABLE 28.—*End-Results in Endarteritis and Thrombo-Angiitis*

Number of cases of primary amputations			27
Died in hospital following amputation		4 or 14.7%	
Cerebral thrombosis	1		
Septicemia	1		
Cause unknown	2		
Died since leaving hospital "heart trouble" (2 years postoperative)		1 or 3.7%	
Alive and reporting		16 or 59.2%	
Wearing appliance and able to work	9		
Totally disabled	7		
Not located		6 or 22.2%	

TABLE 29.—*Tuberculous Lesions Necessitating Amputation*

Situation	No. of Cases	Percentage
Tuberculous infection of the foot or ankle	19	51.4
Tuberculous arthritis of the knee	8	21.6
Tuberculous infection of the hand, wrist, and tendon sheaths	5	13.5
Tuberculous arthritis of the elbow	3	8.1
Tuberculous coxitis	2	5.4

amputations. Of these twenty-eight, or 75.7 per cent, were amputations of the lower extremity and nine, or 24.3 per cent, were of the upper. The proportion of amputations of the upper extremity was higher in tuberculosis then in any other disease group with the exception of the traumatic group.

All of the patients were adults. The ages varied from 18 to 60 years, and the average for the group was 36 years.

The location of the lesions necessitating the amputations is shown in table 29.

The list, however, fails to give any idea of the actual situation and why amputation was resorted to instead of conservative treatment. Excluding the tuberculous lesions of the tarsus and ankle, amputation for tuberculous disease of the joint has been performed at the Massachusetts General Hospital only in exceptional cases. These were usually chronic cases with a duration of many years, and in which not only

extensive tuberculous involvement with multiple sinuses was present, but secondary pyogenic infections as well. They were cases in which conservative treatment had been thoroughly tried and had failed, and in which the general health was being seriously undetermined by the local lesion. Many of the patients were also suffering from advanced pulmonary lesions. In all of the cases the diseased member had long since ceased to have any functional value. In the case of the amputations of the arm, it was only the hopelessness of further conservative treament that led to the final determination to amputate.

In respect to tuberculous lesions of the tarsal joints and ankle in adults, the policy has been different. Here amputation at the middle of the leg has usually been performed as a matter of election. The orthopedic service, which has been responsible for the treatment of most of these patients, has taken the view that when the tuberculous character of the lesion is proved beyond doubt, usually by inoculation of a guinea-pig with aspirated fluid or examination of tissue removed by exploratory incision, then amputation is the treatment of choice. The social and economic conditions surrounding the patients have been the determining factors. The patients treated are wage earners with dependent families and cannot afford long periods of disability. Under the most favorable circumstances a cure cannot be expected from conservative treatment in less than two years, usually longer. The chances of failure are great, and even when successful functional impairment of greater or lesser extent is to be expected. On the other hand, the functional result from a midleg amputation with a good stump is excellent, and the patient ought to be able to do as much work as if a successful result was obtained from conservative treatment. The saving of time is of decisive importance, and in addition there is the improvement in health which may be expected to follow the complete removal of the focus of the disease. It is to be understood, however, that this policy does not apply in the case of children or adolescents in whom the conditions for obtaining a cure are much more favorable and in whose cases the time element is of little importance.

The end-results of amputations for tuberculosis are shown in table 30. Of the thirty-four patients whose cases have been followed up, sixteen have died, or practically 50 per cent. All of these deaths have been due to tuberculous lesions of various types, with the exception of one from septicemia, one from cerebral hemorrhage and one from an unknown cause. Even these diagnoses do not exclude the possibility that death has been due to tuberculosis. Five patients are living, but are under treatment at present for active tuberculosis. In some of the cases new lesions have developed since amputation. Only thirteen of the thirty-four patients who have been traced are alive and apparently well.

The mortality from tuberculosis has been appalling. The date of death is known in fourteen of the sixteen patients who died, and in eleven the fatality occurred within fifteen months after the operation. This suggests that the death had some relation to the operation. On investigation we find that only eight of the thirty-seven patients, or 21.6 per cent, received treatment in a sanatorium after operation, and it is probable that general antituberculous treatment was not carried out as thoroughly as it should have been because it was thought that the focus of disease had been removed. The high mortality figures serve to emphasize the fact that tuberculosis must always be treated as a generalized disease regardless of how localized may be its manifestation. General antituberculous measures must be enforced just as much after amputation as if conservative treatment is being used. On the basis of this study of end-results, the claim that amputation offers a short road to a complete cure cannot be sustained.

TABLE 30.—*End-Results of Amputations for Tuberculosis*

Number of amputations		37
Died in hospital following amputation	2 or 5.2%	
Septicemia	1	
Pulmonary tuberculosis	1	
Died since leaving the hospital	14 or 38%	
Pulmonary tuberculosis	7	
Tuberculous enteritis	2	
Tuberculous meningitis	1	
Tuberculosis of kidney and bladder	1	
Abscess of cervical lymph nodes	1	
Cerebral hemorrhage	1	
Unknown	1	
Alive but suffering from active tuberculous process elsewhere in body	5 or 13.5%	
Alive and apparently well	13 or 35.3%	
Not located	3 or 8%	

Diabetic Gangrene.—There were thirty-six cases of amputation for diabetic gangrene representing 8.5 per cent of the entire series. Twenty-eight of these were primary amputations, and eight reamputations. All of the primary amputations were necessitated by actual gangrene with the exception of one case of persistent ulceration and one in which sepsis was the chief factor. Diabetic gangrene rarely involves the arm, and all of our cases were amputations of the lower extremity; of the thigh, twenty-one, and of the lower leg, fifteen. That diabetic gangrene is usually a disease of old age is borne out by the age incidence of the group, the average being 57.4 years. That there are exceptions to this rule is shown by the fact that the ages varied from 26 to 78 years.

The surgical hazard in these cases is great because of the usually poor physical condition of the patient, the result of the frequent combination of arteriosclerosis, diabetes and sepsis. There were twelve deaths in the hospital, a postoperative mortality of 33 per cent. Reamputation was required in eight cases, or 22 per cent. In five cases this was necessitated by extension of the gangrenous process following primary amputation

below the knee. Two of these patients died. The other reamputations were performed because of unsatisfactory stumps. In addition, two patients had bilateral amputations of the legs at different admissions.

The best treatment for diabetic gangrene is by prevention, as has been pointed out by Joslin,[2] and much may be accomplished along this line. Infection is apparently the match which lights up the process, and this must be avoided at all costs. Every diabetic patient should be informed of the danger of gangrene and advised of the necessity of daily bathing of the feet, of wearing clean hose, of obtaining shoes of correct shape and ample size in order to eliminate corns and ingrowing toe nails of performing routine exercises and finally, of seeking proper surgical care whenever an abrasion of the skin develops.

TABLE 31.—*End-Results in Amputations for Diabetic Gangrene*

Number of cases of primary amputation		36
Died in hospital following amputation	12 or 33.3%	
Diabetes	5	
Bronchopneumonia	3	
Septicemia	2	
Uremia	1	
Pulmonary embolism	1	
Died since leaving the hospital	11 or 30.5%	
Diabetes (11 months, 1½ years, 3 years postoperative)	3	
Cerebral hemorrhage (6 months, 3 years postoperative)	2	
Myocarditis (5 years postoperative)	1	
Carcinoma of breast (1½ years postoperative)	1	
Septicemia (1 year postoperative)	1	
Cause not stated (3 weeks, 1 year, 1½ years postoperative)	3	
Alive but incapacitated from diabetes	2 or 5.5%	
Alive and apparently well	2 or 5.5%	
Not located	11 or 30.5%	

If gangrene appears, amputation should usually be performed early to prevent extension of infection. Amputation of the digits is rarely of any avail except in limited infections or localized areas of ulceration or gangrene. Amputation at the junction of the middle and upper thirds of the lower leg is indicated when the patient is in good general health, pulsation present in the popliteal artery and the infectious process well localized. When the patient is elderly or shows evidence of extensive arteriosclerosis, even though the gangrene involves only the forefoot, nothing short of amputation above the knee will suffice, and the Gritti-Stokes amputation provides the best stump in such cases when it can be performed. When the entire foot is affected, amputation above the knee should be performed. In five of our diabetic patients the mistake was made of amputating below the knee, with the result that the gangrene extended, reamputation above the knee became necessary, and two of the patients died.

2. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923.

Most of the risk of operation in diabetic patients has been removed by the discovery of insulin. The cooperation of an internist is of invaluable assistance, and medical supervision should go hand in hand with the surgical care. With skilful medical treatment, the surgeon may now disregard the diabetic factor as far as the operation is concerned.

Insulin came into use in 1923, and we have been interested to analyze the end-results in our cases of diabetic gangrene with reference to this date. Actually, the figures are disappointing, as the death rate appears to be about the same before and after the use of insulin, but we are convinced that in a larger group of cases the results would be different.

In the group of thirty-six amputations there were twelve deaths in the hospital, and eleven patients have died since discharge from the hospital. These are divided as shown in table 32.

The end-results are known in only twenty-seven of the thirty-six cases (table 31), but it is certainly a striking fact that of this number only four patients are alive and only two are able to report themselves in

TABLE 32.—*Deaths Before and After the Use of Insulin*

	Before Insulin Therapy	Since use of Insulin
Number of amputations	19	12
Hospital deaths	7	6
Deaths since discharge	6	2*
Total deaths	13 or 68.4%	8 or 66%

* Amputated before insulin, but have died since.

good health. Diabetic gangrene would appear to be of ominous portent even for those who survive the operation.

Arteriosclerotic Gangrene.—Amputations for arteriosclerotic gangrene, excluding the diabetic cases, numbered thirty-six and constituted 8.5 per cent of the entire series. Of these, thirty-two were primary amputations and the remainder reamputations. Most of the patients were of advanced age, the average for the group being 66.3 years. The youngest patient was a man, aged 32, the diagnosis was based on the pathologic examination of the amputated specimen, which showed precocious arteriosclerosis. The oldest patient was aged 88. The postoperative hospital mortality was 22.2 per cent which is in keeping with the poor surgical risk which these cases represent.

Arteriosclerotic gangrene occurs almost exclusively in the lower extremity, and amputations of the lower limb were performed in all of our cases. In this condition, there is practically no alternative to amputation above the knee. In twenty-nine of our cases, or 80 per cent, amputations of the thigh were performed, and there were only seven in which amputations of the lower leg was employed. Three of the latter required reamputation because of extension of the gangrene so that the

original amputation below the knee had been a mistake. The fourth reamputation was performed in a case in which primary traumatic amputation had been performed many years before, and in which gangrene subsequently developed in the stump of the lower leg, so that reamputation above the knee was necessary. On the whole, the evidence obtained from study of this group justifies the conclusion that arteriosclerotic gangrene always necessitates amputation above the knee. The blood supply in the region of the knee is usually abundant even in these cases, and both from the standpoint of actual clinical experience and from a knowledge of the functional results that may be obtained, we advise the Gritti-Stokes amputation whenever possible.

The end-results have been ascertained in sixteen of the twenty-eight patients discharged from the hospital (see table 33). Six have died within two years of the operation, two are alive but suffering from auricular fibrillation, and eight are alive and apparently well. The func-

TABLE 33.—*End-Results in Amputations for Arteriosclerotic Gangrene*

Number of cases of amputation			36
Died in hospital following amputation		8 or 22.2%	
Bronchopneumonia	3		
Causes undetermined	4		
Septicemia	1		
Died since leaving the hospital		6 or 16.6%	
Arteriosclerosis (6 months, 1½ years, 2½ years postoperative)	3		
Cerebral hemorrhage (3 weeks, 7 months postoperative)	2		
Chronic nephritis (2 years postoperative)	1		
Alive but suffering from auricular fibrillation		2 or 5.5%	
Alive and apparently well		8 or 22.2%	
Not located		12 or 33%	

tional results are poor because of old age and feebleness. Only a few are making use of appliances. Of the twenty-four patients whose cases have been followed, fourteen, or 58 per cent, are dead, two are incapacitated, and only eight, or 33 per cent, are in good health. However high this mortality may appear, it is doubtful if it is much above what should be expected in a group of persons of similar age.

Sarcoma.—Thirty amputations were performed for sarcoma, representing 7.1 per cent of all amputations studied. Twenty-eight of these were primary amputations, one was a reamputation, and one was a case of multiple amputation at separate admissions which has been counted twice. The average age for the group was 31.4 with extremes of 10 and 69 years.

The classification of the tumors and their location are shown in table 34, also the results so far as it has been possible to ascertain them.

The amputations were distributed as follows: thigh, twenty-one; lower leg, three, and upper arm, six. Amputations of the thigh was performed in fourteen cases of tumor of the femur, in one of fibrosarcoma of the thigh, and in six of seven cases of tumor of the tibia, the

exception being a case of giant cell tumor. The three amputations of the lower leg were the result of giant cell tumor of the tibia, and one case each of melanotic sarcoma and angiosarcoma of the foot. Amputation of the upper arm was due to sarcoma of the hand in five cases and to fibrosarcoma of the forearm in one case. There was one case of reamputation due to the recurrence of a chondrosarcoma in the stump following a primary amputation at midthigh three years earlier. At the second admission, the hip joint was disarticulated; notwithstanding this, the patient died of pulmonary metastsis one year later. In addition, three amputations of different limbs were performed on one patient at three different times. This was a remarkable case with a pathologic diagnosis of osteochondrosarcoma. The primary tumor was situated at the right elbow, and amputation of the humerus was performed in 1904. The patient remained well until 1923, when he was readmitted with a diag-

TABLE 34.—*Thirty Cases of Sarcoma, Type and Location of Tumor, Results*

	Tumors of Bone			Tumors of Soft Parts					Results			
Type of Tumor	Femur	Tibia	Humerus	Foot	Hand	Forearm	Thigh	Total	Dead	Alive and Well	Alive but Show Recurrence	Not Located
Giant cell tumor	..	1	..	..	..	..	..	1	..	1	..	..
Osteogenic sarcoma	9	2	2	..	..	..	..	13	5	4	..	2
Sarcoma unclassified	5	4	3	..	1	..	..	12	6	2	1	3
Fibrosarcoma	..	..	..	..	..	1	1	2	..	..	1	1
Angiosarcoma	..	..	..	1	..	..	..	1	..	1	..	..
Melanotic sarcoma	..	..	..	1	..	..	..	1	..	..	1	..
	14	7	4	2	1	1	1	30*	11	8	3	6

* Two patients had secondary amputations for recurrent tumor.

nosis of osteogenic sarcoma of the left tibia, and midthigh amputation was performed. He was readmitted in 1925 because of a similar tumor in the lower end of the right femur, and the right thigh was amputated. This patient is still living.

There was no operative fatality, and all of the patients left the hospital alive. The results subsequent to discharge are shown in table 35. In view of the grave prognosis in these cases, we are on the whole cheered to find eight patients still alive and well. From the prosthetic standpoint, the results are satisfactory, and it has not been necessary to reamputate in any case because of an unsuitable stump.

Carcinoma.—There were eleven cases of amputation for carcinoma, 2.6 per cent of the entire sereis. The tumors were classified as follows: epithelioma, ten cases; metastatic hypernephroma of the femur, one case. One epithelioma developed in an osteomyelitis sinus of an amputation stump, the primary amputation having been performed for trauma. Two epitheliomas of the hand were the result of exposure to the

roentgen ray. The ages of the patients varied from 36 to 65 years, with an average of 53.7 years. The amputations were distributed as follows: lower leg, four; thigh, three; forearm, three, and upper arm, one.

There were no deaths as a result of operation and no reamputations. Three of the eleven patients have died since leaving the hospital, one of

TABLE 35.—*End-Results in Amputations for Sarcoma*

Number of amputations for sarcoma		30
Reamputations because of recurrent tumor		1
Secondary amputations of opposite limb		1
Total cases		28
Died in hospital following amputation	0	
Died since leaving hospital	11 or 40%	
Metastatic sarcoma (2 cases 4 months, 6 months, 8 months, 1 year, 2 years, 2½ years, 7 years postoperative)	8	
Appendicitis (17 months postoperative)	1	
Cerebral hemorrhage (3½ years postoperative)	1	
Not stated (1½ years postoperative)	1	
Alive, but have recurrence or metastatses	3 or 11%	
Alive and clinically well	8 or 28%	
Osteogenic sarcoma, shaft of humerus, 6 years postoperative		
Osteogenic sarcoma, shaft of humerus, 1½ years postoperative		
Osteogenic sarcoma, lower end of femur, 5 years postoperative		
Osteogenic sarcoma, shaft of femur, 3 years postoperative		
Sarcoma, unclassified, lower end of femur, 6½ years postoperative		
Sarcoma, unclassified, lower end of femur, 3 years postoperative		
Giant cell tumor, upper end of tibia, 10 years postoperative		
Angiosarcoma, dorsum of foot, 1 year postoperative		
Not located	6 or 21%	

TABLE 36.—*End-Results of Amputations for Carcinoma*

	No. of Cases	Post-operative Period	Dead	Alive and Well	Alive but Show Recurrence	Not Located
Metastatic hypernephroma	1	2½ yrs.	1	0	0	0
Epithelioma, amputation stump, foot	1	1½ yrs.	..	1	0	..
Epithelioma of hand, metastases to axilla	1	9½ yrs.	..	..	..	1
Epithelioma of hand	1	9 yrs.	..	..	..	1
Epithelioma of fingers, metastases to axilla	1	8½ yrs.	1	..	..	..
Epithelioma of thigh	1	1½ yrs.	..	1	..	..
Epithelioma of hand	1	10 mos.	1	..	..	..
Epithelioma of lower leg	1	5 yrs.	..	1	..	..
Epithelioma of foot	1	1 yr.	..	1	..	..
Epitheloima of hand	1	.....	..	..	..	1
Epithelioma of hand	1	.....	..	..	..	1
Totals	11		3	4	0	4

uremia and two of metastatic carcinoma (table 36). Of the latter, one died two and one-half years after amputation, and the other eight and one-half years; four of the patients are clinically well, and four have not been found.

Thombosis and Embolism.—There were ten amputations in nine cases on account of thrombosis and embolism, 2.3 per cent of the entire series. All of these were in elderly patients. Three cases were diagnosed embolism and the remainder thrombosis. In two cases of throm-

bosis, and in all cases of embolism there was an associated diagnosis of arteriosclerotic heart disease, and this, presumably, was the source of the thrombus. One case of thrombosis occurred during convalescence from pneumonia. Embolectomy was performed in one case of sudden obstruction of the brachial artery but was unsuccessful in reestablishing the circulation, and amputation was necessitated later. Gangrene was present in several instances, and it is difficult to differentiate these cases from arteriosclerotic gangrene. Most of the amputations were of the lower leg, being distributed as follows: thigh, seven; lower leg, two, and upper arm, one.

There were two deaths in the hospital, one from cardiac failure and the other from bronchopneumonia (table 37). Three patients have died since discharge from the hospital, one from cerebral hemorrhage and two from cardiac lesions. Of the other four patients, three are alive and well, and one has not been located. Two of the survivors show good functional results and are working; the third has suffered total disability.

TABLE 37.—*End-Results of Amputations for Thrombosis and Embolism*

Number of cases (10 amputations)		9
Died in hospital	2 or 22%	
Cardiac failure	1	
Bronchopneumonia	1	
Died since leaving hospital	3 or 33%	
Myocardial failure (3 weeks postoperative)	1	
Cerebral hemorrhage (1 year postoperative)	1	
Valvular heart disease (6 years postoperative)	1	
Alive and apparently well	3 or 33%	
Not located	1 or 12%	

Miscellaneous.—Gas Bacillus Infection: (Eight cases, eight amputations, 1.9 per cent.) All but one of the cases of gas bacillus infection developed following traumatic injury; five were compound fractures, one was a case of traumatic amputation, and one was an injury of a soft part. The striking fact about these cases is that in every one the risk of closing the wound by primary suture had been taken. The infection manifested itself in from three to fourteen days. The remaining case was that of a feebleminded child with an ulcerated foot due to syringomyelia. There was no history of injury, and the infection developed spontaneously, probably from lack of proper care of the wound. The open type of amputation was performed in each instance. Three cases terminated fatally, or 37 per cent.

Ununited Fractures: (Four cases, four amputations, 0.9 per cent.) Amputation was performed in cases of ununited fracture only because some pathologic process was present which prevented union and the patients were of such advanced age that a rapid solution of their problems was necessary. In one case there was a fracture of the shaft of the

femur in a tabetic person, in a second case of fracture of the tibia in a man, aged 56, with syphilitic osteitis, in a third case an ununited fracture of the femur with failure to obtain union after four years of conservative treatment and in a fourth case of osteomyelitis with failure of union following spontaneous fracture. No deaths occurred while the patients were in the hospital, although one of the patients died after discharge. The three remaining patients are alive and in good health.

Ruptured Brachial Plexus: (Three cases, three amputations, 0.7 per cent.) Amputation of the humerus or disarticulation of the shoulder was performed in three cases of traumatic rupture of the brachial plexus with complete paralysis of the arm. Each of these cases was of several years' duration, and reparative operations had been performed without success. The amputation was performed in each instance at the patient's request. In two cases this was because of obstinate and severe nerve pain, in the

TABLE 38.—*End-Results of Amputations for Miscellaneous Conditions*

Condition	Number of Cases	No Amputation	Post-operative Deaths	Deaths Since Leaving Hospital	Patients Alive	Not Found
Gas bacillus infection....	8	8	3	0	4	1
Ununited fracture.....	4	4	0	1	3	0
Ruptured brachial plexus	3	3	0	1	2	0
Spina bifida.....	1	3	0	1	0	0
Charcot joint.....	1	2	0	0	1	0
Foot deformity.....	1	1	0	0	1	0
Trophic ulcer.....	1	1	0	0	1	0
Tetanus.....	1	1	1	0	0	0
Pressure of pelvic tumor.	1	1	0	1	0	0
Ligation for aneurysm...	1	1	0	0	1	0
	22	25	4	4	13	1

third because the arm represented a useless and constant source of annoyance. In one of the cases in which pain was present the patient was relieved; in the other case, he was not. In the latter, injection of alcohol into the nerve roots was subsequently performed, and later an interthecal division of the dorsal roots, without much improvement. This patient died of nephritis; the other two are living and well.

Spina Bifida: (One case, three amputations, 0.7 per cent.) This was a case of paraplegia due to spina bifida with equinovarus deformity of the feet and trophic ulcers. Bilateral Syme's amputation was performed, but trophic ulcers appeared on the stumps, and it was subsequently necessary to amputate at midleg.

Charcot Joint: (One case, two amputations, 0.4 per cent.) Amputation was first performed at midleg because of a Charcot ankle. Later a Charcot arthropathy developed in the opposite knee, and it was necessary to amputate in the lower third of the thigh. This patient gets around well with his appliances and is able to earn a living.

Foot Deformity: (One case, one amputation, 0.2 per cent.) This was a case of burn of both feet by hot metal with scar contracture and deformity. Syme's amputation was performed.

Trophic Ulcer: (One case, one amputation, 0.2 per cent.) This was a case of perforating ulcer of the foot not amenable to treatment. Mid-leg amputation was performed, with relief.

Tetanus: (One case, one amputation, 0.2 per cent.) This was a case of compound fracture of both bones of the leg; the patient had been treated elsewhere and transferred to the Massachusetts General Hospital ten days after injury. Tetanus antitoxin had not been administered. Tetanus developed on the twelfth day and was severe. Antitoxin was given intravenously and intraspinally, and the leg was amputated at midthigh. The case terminated fatally.

Pressure of Pelvic Tumor: (One case, one amputation, 0.2 per cent.) A woman, aged 55, had sarcoma of the uterus and two weeks before admission, developed gangrene of the right foot and leg. It was thought that this was due to the pressure of the tumor mass on the iliac vessels.

Gangrene After Ligation for Popliteal Aneurysm: (One case, one amputation, 0.2 per cent.) This was a case in which the popliteal artery was ligated for aneurysm. Gangrene developed in the foot twenty-two days later, and amputation was performed at the middle of the leg.

SUMMARY

General.—In a survey at the Massachusetts General Hospital covering the decade from 1916 to 1926 amputations constituted 1 per cent of all operations, and 0.64 per cent of all hospital admissions. The most common causes of amputation were trauma and sepsis which together accounted for 37 per cent of the cases. The hospital mortality following amputation was 11.6 per cent. Forty per cent of the deaths were due to shock and septicemia. Postoperative complications were noted in 167 of 420 cases, of which 20.8 per cent were wound infections, 2.4 per cent bronchopneumonia, 1.9 per cent extending gangrene, 0.4 per cent pulmonary embolism. Postoperative hemorrhage occurred in only two cases.

Approximately 12 per cent of the amputations were performed by the open, flapless method, and the remainder were closed. Of the amputations followed by closure of the wound, drains were inserted in 72 per cent, and in 28 per cent drains were not used. The patients on whom amputation was performed by the open method were free from acute septic complications. When amputation is necessitated by sepsis or trauma, the open method appears to be safer, and it also conserves the

length of the stump. Drains are often used needlessly, and many persisting sinuses can be traced to this cause.

Functional Results.—Sixty-seven per cent of the patients with amputations of the thigh used appliances. The longer the stump the better were the results obtained. Much benefit was noted from the use of temporary prosthesis. The average time between the operation and the delivery of the permanent limb was 13.3 months when temporary prosthesis had not been used, but when one had been fitted, this period was shortened to 5.5 months. Fifty-three per cent of the patients with amputations at the thigh were employed.

Eighty-five per cent of the patients with amputations of the lower leg used appliances. The functional results were usually better than after amputations of the thigh, although a larger proportion of the patients complained of stump disabilities. The temporary prosthesis was of benefit, but its use reduced the time interval between operation and the delivery of the permanent limb less than in the case of amputations of the thigh.

The results of the Syme amputation were satisfactory in five of six patients. All had stumps capable of direct end-bearing, and the majority were doing heavy work.

In patients in whom amputations of the upper extremities had been performed, the length of the stump made little difference as far as the functional result was concerned. Appliances were used by only six of thirty-four patients. Seventy-eight per cent of the patients in whom amputations of the upper arm had been performed were working, but the occupations were of a type which did not require the use of both hands. On this showing, it would appear that little heed should be given to prosthetic considerations in determining the level of amputation in the upper extremity.

Reamputations.—Of the 360 primary amputations performed at the Massachusetts General Hospital, reamputation was required in fifty-three cases, or 14.7 per cent. First intention healing was obtained in only 42 per cent. Painful nerve bulbs constituted an unimportant cause of reamputation. This result is probably to be attributed to the employment of the alcohol injection technic. The most common cause of reamputation was ulcer of the stump. Amputations of the lower leg had been performed on seventeen of twenty-one patients with ulcerated stumps and amputations of the thigh on four. In eleven patients it was necessary to reamputate above the knee because of extending gangrene following a primary amputation of the lower leg.

Disease Groups.—Traumatic amputations were twice as common as amputations from any other cause. These were distributed fairly evenly between the two segments of the upper and lower limb. Trauma

accounted for fifty, or 61 per cent, of the eighty-one amputations of the upper extremity performed for all causes.

Most of the amputations for sepsis were performed on the lower limb.

In amputations for thrombo-angiitis obliterans and endarteritis, the results were unsatisfactory chiefly because of progression of the disease, involvement of other limbs and the necessity of repeated amputations.

In amputations for tuberculosis, a large number of the patients died of tuberculous complications within two years of amputation. This was apparently due to the fact that general antituberculous measures were not carried out after the operation.

When amputation was performed for diabetic gangrene, only a few of the patients survived for more than a few years.

In both diabetic and arteriosclerotic gangrene, the best functional results were obtained with the Gritti-Stokes amputations.

Eight of twenty-eight patients on whom amputation was performed for sarcoma have remained well for a number of years, indicating that the prognosis after amputation is better than has been generally thought.

RELATION OF THE PARATHYROIDS TO THE HEALING OF A FRACTURE AS CONTROLLED BY THE ROENTGEN RAYS*

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Since Sandström's discovery of the external parathyroids in 1880, the parathyroid glands have been discussed extensively.

There are two schools of thought, one being that these glands influence calcium metabolism, and the other that they exert a detoxicating effect on guanidin bodies. The balance of opinion seems to favor the former, and in 1925, definite evidence as to their influence on calcium metabolism was established by Collip,[1] and by Collip, Clark and Scott.[2]

While engaged in an attempt to produce by means of partial parathyroidectomies a condition in the bones of experimental animals analogous to idiopathic osteopsathyrosis in man, it occurred to me that it would be interesting to note the effect of parathyroidectomy, partial or complete, on the healing of fractures.

Morel[3] (1909-1910) working with cats, and Canal (1919) working with rats, asserted that removal of the parathyroids causes a delay in the healing of fractures. The recorded experiments of these authors, however, leave one in doubt as to the amount and nature of the tissue removed.

Ogawa[4] (1925) published the results of a chemical analysis of the callus deposited at the site of fractures in rats which had had their parathyroids either entirely or almost entirely destroyed by cauterization. He found that the calcium content of the callus was decreased in these animals as compared with his controls. He further adduced that destruction of the thyroid did not have any deleterious effect on the healing of fractures.

In 1926, I decided to repeat the experiments of these men, using more elaborate precautions. Thus it seemed necessary to study the effect of excision of different amounts of parathyroid tissue, to verify the condition of the fracture at different intervals by roentgen-ray examination, and to make determinations of the blood calcium during the course of the several experiments.

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* From the Department of Physiology and Experimental Medicine, McGill University. The expenses of this research were defrayed by the Percy Cowans Scholarship.

1. Collip: J. Biol. Chem. **63**:395, 1925.
2. Collip, Clark and Scott: J. Biol. Chem. **63**:439, 1925.
3. Morel: Compt. rend. Soc. De Biol. **68**:163, 1910.
4. Ogawa: Arch. f. exper. Path. u. Pharmakol. **109**:83, 1925.

EXPERIMENTAL WORK

Cats were chosen for the experiments. There are four parathyroids in these animals, two internal and two external. The internal lie buried in the thyroid, one in each lobe and are situated near the upper pole. The external lie on the outer surface of the thyroid near the upper border; their exact situation, however, may vary. They are small bean-shaped bodies somewhat paler than the thyroid and are about 7 mm. long by 4 mm. broad.

All operations were aseptically performed under sodium iso-amyl-ethyl barbituric acid anesthesia (0.5 cc. per kilogram of body weight administered intraperitoneally).

An incision was made beginning half an inch above the thyroid cartilage and extending down over the trachea for about 3 inches (7.6 cm.). In this manner the ribbon muscles of the neck were exposed. These were retracted, thus bringing the trachea into the field of operation. The thyroid lobes could then be delivered at the surface of the wound and as many parathyroids as required extirpated. After tying off all bleeding points, the thyroid was allowed to fall back into the normal position. The retracted muscles were brought together and held by catgut sutures, and the skin was closed by black silk, a collodion dressing then being applied. By means of a small Thomas wrench a simple fracture was then produced in the left radius and ulna, and the leg put up in a starch bandage for forty-eight hours, or until the animal had completely recovered from the anesthesia.

Blood calcium determinations by the Tisdall-Kramer method were made previous to the operation and at various periods subsequently.

In this manner about thirty cats of various ages were operated on in series of threes: one, the control, was simply subjected to a fracture of the left radius and ulna; another had two parathyroids removed either from the same side or one from each side; while the third had three parathyroids extirpated. Removal of an internal parathyroid always necessitated excision of some of the thyroid tissue along with it. In some instances the whole thyroid lobe together with its two parathyroids was extirpated.

By making successive microscopic sections of the tissues removed at operation one obtained a check on the number of parathyroid glands excised. When the animals were killed, a further careful examination of the remaining thyroid tissue was made, in order to be sure of the number of parathyroids extirpated.

EXPERIMENTS

SERIES 1.—*Cat A.*—Jan. 15, 1926: Right thyroparathyroidectomy was performed on a young female cat; two parathyroids were identified in the tissue removed. The left radius and ulna were fractured in the middle third. A starch bandage was applied and a roentgenogram taken.

Jan. 17: The bandage was removed. The animal took its food well and did not show any evidence of tetany. Between January 17 and January 27 the animal remained normal, but refused to put its weight on the left leg. On the latter date there appeared to be slight mobility at the site of the fracture, as tested by handling, although the leg was used to some extent in walking.

Jan. 29: A roentgenogram showed trace of callus at the site of fracture. The animal bore its weight on the injured limb. There was little, if any, praeternatural mobility on handling.

Feb. 5: The injured limb was used readily and with little perceptible limp. There was a definite deposition of callus, as shown by a roentgenogram.

The animal was killed on this day and sections made of the remaining thyroid, in which two parathyroids were found. No trace of other parathyroid tissue was present. At no time between January 15 and February 5 did the blood calcium go below 10 mg. per one hundred cubic centimeters of serum.

Cat B.—Jan. 15, 1926: A young female cat was used. The blood calcium was 10.5 mg. per hundred cubic centimeters of serum. Thyroparathyroidectomy was performed on the left side and external parathyroidectomy on right side, i. e., three parathyroids were removed.

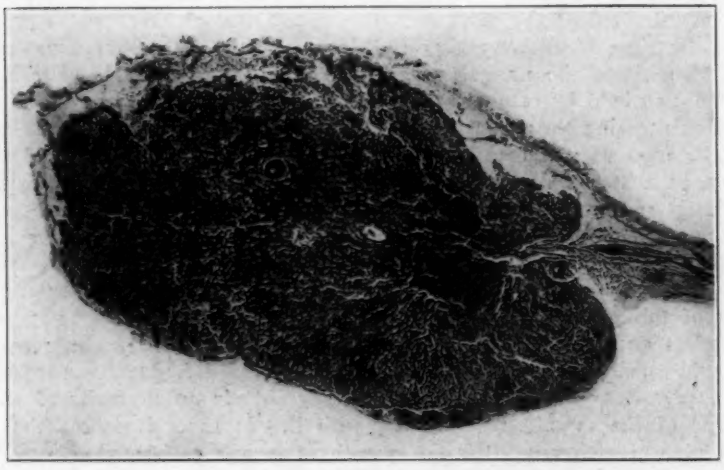

Fig. 1.—External parathyroid in a cat.

The left radius and ulna were fractured. A starch bandage was applied.

Jan. 17: The bandage was removed. The cat appeared more sickly than cat A, but there was no evidence of tetany. She moved about the cage with the left leg held off the floor and took a little food.

Jan. 19: The blood calcium was 8.7 mg. per hundred cubic centimeters of serum.

Jan. 22: The leg was still held off the floor when walking. The cat ate quite well.

Jan. 29: A roentgenogram did not show any evidence of callus. The blood calcium was 8.7 mg. per hundred cubic centimeters of serum.

Jan. 31: One gets the impression of there being a pseudo-arthrosis at the site of the fracture.

Feb. 5: There was still no evidence of callus shown by the roentgen-ray. The blood calcium was 8.5 mg. per hundred cubic centimeters of serum.

Feb. 10: The praeternatural mobility not so marked as previously and the animal put her foot to the floor of the cage, although she bore little weight on it. The blood calcium was now 10.2 mg. per hundred cubic centimeters of serum.

Feb. 24: The blood calcium was 10.4 mg. per hundred cubic centimeters of serum. The animal bore weight on her leg. There was slight limp. On palpation there was apparent evidence of callus formation. This was confirmed by a roentgenogram.

March 1: The animal bore her weight on the injured leg, and walked with a scarcely perceptible limp. On this date she was killed. Microscopic examination of the remaining thyroid showed the presence of the single internal parathyroid embedded in the thyroid tissue.

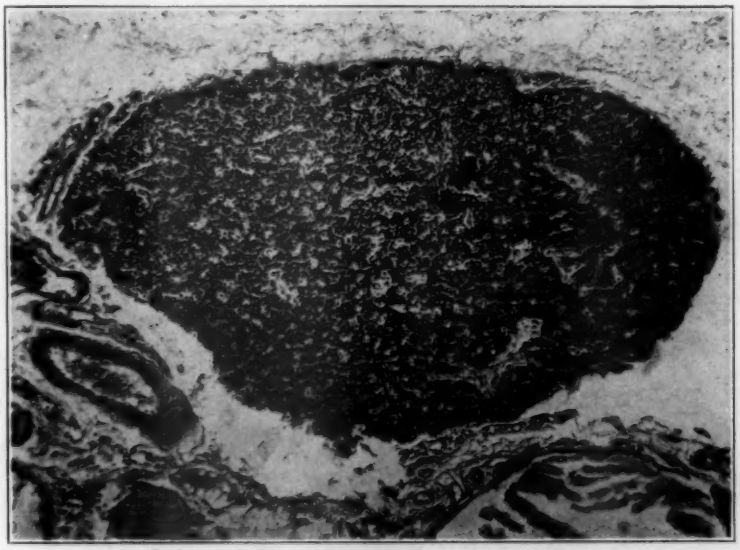

Fig. 2.—Internal parathyroid with thyroid in a cat.

Cat C.—Jan. 15, 1926: A young female cat was used for a control for cat *A* and *B*, series 1. The left radius and ulna were fractured. A starch bandage was applied.

Jan. 17: The bandage was removed. The rate of healing of the fracture in this case was similar to that described in cat A of this series. The first slight indication of callus by a roentgenogram was on January 9.

Feb. 5: Definite evidence of callus was found. The foot was applied to the floor of the cage without any hesitation and there is no noticeable limp.

SERIES II.—*Cat A.*—Feb. 17, 1926: An adult female cat was used with a blood calcium 10.5 mg. per hundred cubic centimeters of serum.

Left external parathyroidectomy and right thyroparathyroidectomy was performed, i. e., three parathyroids were removed. The left radius and ulna were fractured. A starch bandage was applied.

Feb. 18: The animal recovered completely from anesthetic. There was no evidence of tetany. She took little food. The bandage was removed.

Feb. 24: The blood calcium was 8.2 mg. per hundred cubic centimeters of serum. Her general health was good.

March 3: The animal was in good health. The injured leg was not put to the floor when walking. The blood calcium was 9 mg. per hundred cubic centimeters of serum.

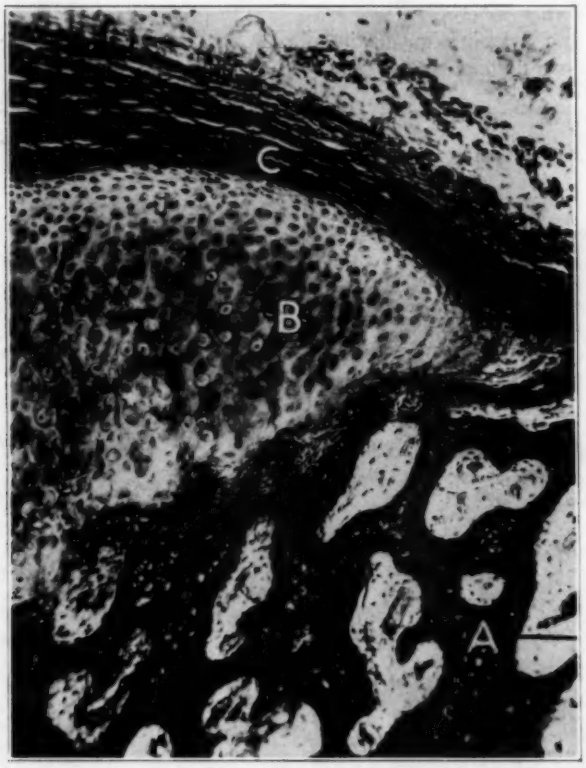

Fig. 3.—Stage in the healing of a fracture in a normal cat ten days after the break. *A* indicates new formation; *B*, cartilage, and *C*, connective tissue which runs from the surface of one fragment to the other.

March 8: There was not any evidence of union as tested by handling. A roentgenogram did not show any callus formation.

The animal was killed on this date. Enclosing the fractured ends was a tough fibrous capsule-like structure, which offered no gritty resistance to a scalpel. This capsule, while preventing separation of the ends one from another, when the two fragments (after removal of the muscles) were pulled apart, nevertheless, allowed of considerable angulation of the two pieces in any direction whatsoever.

Cat B.—Feb. 17, 1926: An adult female cat was used with a blood calcium of 10 mg. per hundred cubic centimeters of serum. One external parathyroid was removed from each side. The left radius and ulna were fractured. A starch bandage was applied.

Feb. 19: The cat took food. The fractured leg was held off the floor. There was not any evidence of tetany. The bandage was removed.

Feb. 24: The blood calcium was 9.9 mg. per hundred cubic centimeters of serum.

Fig. 4.—Stage in the healing of a fracture in a young cat sixteen days after the break. *A* indicates new bone; *B*, connective tissue, and *C*, fibro-cartilage.

March 3: There appeared to be some attempt at union, as tested by handling. The injured leg, although put to the ground, was not used for any perceptible amount of weight bearing. The blood calcium was 10.2 mg. per hundred cubic centimeters of serum.

March 8: On manipulation there appeared to be firm union at the site of fracture and the animal bore weight on all four legs. A roentgenogram showed definite deposition of callus at the site of fracture. The animal was killed for examination.

Cat C.—Feb. 17, 1926: An adult female cat was used as the control for cat A and B, series II. The left radius and ulna were fractured. A starch bandage was applied.

Feb. 19: The bandage was removed. The animal was apparently not suffering any ill effects.

Feb. 24: No attempt had been made as yet to bear weight on the fractured leg.

March 3: The leg was put to the ground, but little weight bearing was attempted. Manipulation revealed some degree of union. A roentgenogram showed a slight amount of callus.

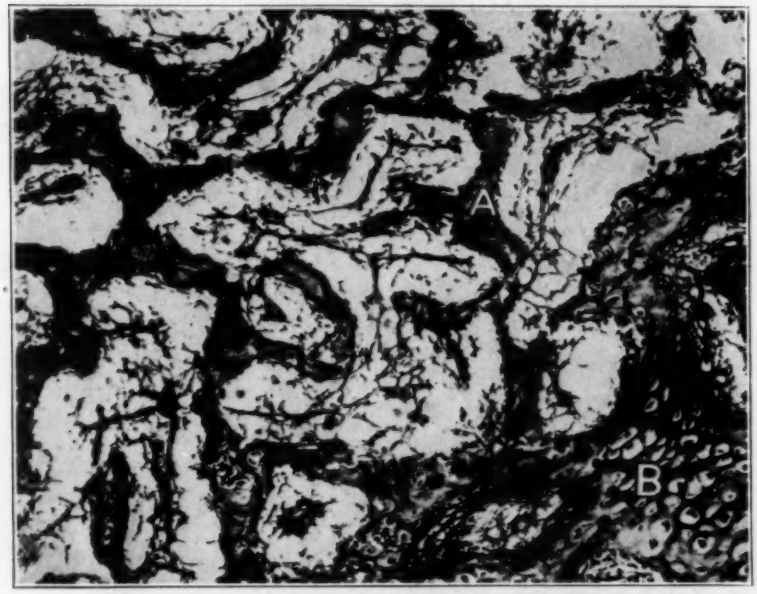

Fig. 5.—Section of the membrane uniting a fracture in a normal cat twenty-three days following the break. *A* indicates new bone, and *B*, cartilage. Compare this figure with figure 6.

March 8: Union was firm and a roentgenogram showed definite callus deposition.

SERIES III.—*Cat A.*—March 28, 1926: An adult female cat with a blood calcium of 10.8 mg. per hundred cubic centimeters of serum was used. Thyroparathyroidectomy of left side and external parathyroidectomy of the right side was performed. The left radius and ulna were fractured. A starch bandage was applied.

March 25: There was not any evidence of tetany. The animal took food freely.

March 30: The broken leg was held off the floor. Praeternatural mobility was present. The blood calcium was 8.7 mg. per hundred cubic centimeters of serum.

April 10: There was no clinical evidence of union of fracture, otherwise the cat appeared normal.

April 20: There was still no evidence of union.

April 30: The blood calcium was 10.2 mg. per hundred cubic centimeters of serum. Manipulation revealed evidence of slight bony union.

May 11: A roentgenogram showed definite callus formation, although it was apparently less in amount than in the control animal, series III, B. The blood calcium was 11 mg. per hundred cubic centimeters of serum. (It is interesting to note that this animal became pregnant at a later date and died in tetany.)

Fig. 6 (cat 101).—Section of the membrane formed at the site of the fracture twenty-three days after the break. *A* indicates connective tissue; *B*, new blood vessel and *C*, cartilage. Note that no new bone formation is seen in this section.

Cat B.—March 23, 1926: An adult female cat with a blood calcium of 10.8 mg. per hundred cubic centimeters of serum was used. One external parathyroid was removed from each side. The left radius and ulna were fractured. A starch bandage was applied.

March 25: The animal took food freely. There was not any evidence of tetany. The bandage was removed.

March 30: The broken leg was held off the floor. The blood calcium was 10.7 mg. per hundred cubic centimeters of serum.

April 10: The injured leg was now put to the floor and the animal moved about freely. Union was apparently firm, as tested by handling. The blood calcium was 11 mg. per hundred cubic centimeters of serum.

Cat C.—March 23, 1926: An adult female cat was used as a control animal for cats A and B, series III. The left radius and ulna were fractured and a starch bandage applied.

March 25: The bandage was removed.

April 10: The animal put its foot to the ground without hesitating; union appeared to be firm.

May 11: There was a definite deposition of callus at the site of the fracture; the animal moved about easily and without inconvenience. The blood calcium was determined on three different occasions and was never below 10 mg. per hundred cubic centimeters of serum.

SERIES IV.—*Cat A.*—March 11, 1927: An adult female cat with a blood calcium of 11.7 mg. per hundred cubic centimeters of serum was used. Both parathyroids were removed from the left side. One parathyroid was removed from the right side. The left radius and ulna were fractured. A plaster bandage was applied.

March 12: The animal had not entirely recovered from the anesthetic.

Figure 7

Figure 8

Fig. 7 (series I, cat A).—Twenty-one days after fracture. The arrow indicates callus.

Fig. 8 (series I, cat B).—Twenty-one days after fracture.

March 13: The bandage was removed. The animal recovered from anesthesia. There was not any evidence of tetany. She took food and did not attempt to apply the broken leg to the floor.

March 14: The blood calcium was 8.3 mg. per hundred cubic centimeters of serum. The animal appeared to be in good health and moved about the cage on three legs.

March 17: The blood calcium was 8.4 mg. per hundred cubic centimeters of serum. There was not any evidence of tetany. The general health of the cat appeared to be excellent.

March 22: The animal's health remained excellent. There was no evidence of union of fracture, as tested by handing; nor did the animal attempt to apply the injured leg to the ground. The neck wound was completely healed; there was no infection.

March 30: The animal still walked on three legs. There was no evidence of bony union of the fracture. A roentgenogram showed a slight haziness at the site of the fracture, but no definite callus formation.

March 31: The blood calcium was 9.6 mg. per hundred cubic centimeters of serum. The animal walked on three legs. There was no evidence of bony union, as tested by handling.

April 5: The general health of the animal was good. The broken leg gave one the impression of a pseudoarthrotic joint.

Figure 9

Figure 10

Fig. 9 (series I, cat C).—Twenty-one days after fracture. The arrow indicates callus.

Fig. 10 (series II, cat A).—Nineteen days after fracture.

April 10: The animal walked on three legs and did not attempt to bear any weight on the injured limb.

April 15: There was no appearance of bony union. The general health of the animal was good.

April 18: The blood calcium was 10.2 mg. The mobility at the site of the fracture was not so marked as previously. The animal now put the leg to the floor.

May 2: This animal is still alive and now has firm bony union, as tested by handling.

Cat B.—March 11, 1927: An adult female cat with a blood calcium of 11 mg. per hundred cubic centimeters of serum was used. Both external and internal parathyroid were removed from the right side, together with half of the upper third of the right thyroid. The left radius and ulna were fractured. A starch bandage was applied.

March 12: The animal had not completely recovered from the anesthesia.

March 13: There was not any evidence of tetany. The bandage was removed. The animal took food.

Figure 11

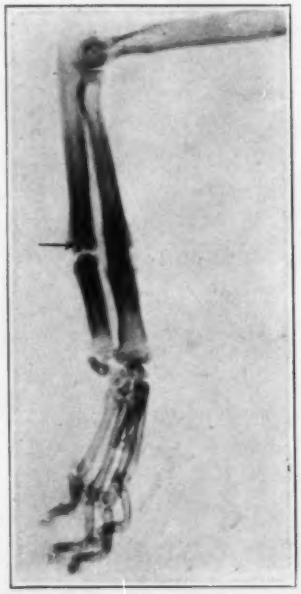

Figure 12

Fig. 11 (series II, cat B).—Nineteen days after fracture. The arrow indicates callus.

Fig. 12 (series II, cat C).—Nineteen days after fracture. The arrow indicates callus.

March 14: The general health was good. The blood calcium was 10.8 mg. per hundred cubic centimeters of serum. The animal did not apply the broken leg to the ground.

March 17: The cat had not as yet put the injured leg to the ground in walking.

March 22: She put her weight on the broken leg. A certain amount of thickening at the site of fracture was perceptible. Angulation of fragments occurred if lateral pressure was applied.

March 30: She walked with a slight limp. When jumping from a height of from 4 to 5 feet she used both front legs to alight on. Union, as tested by handling, was firm.

April 5: The union was solid and the animal moved about freely.

Cat C.—March 11, 1927: An adult female cat was used as control for cats A and B, series IV. The blood calcium was 10.8 per hundred cubic centimeters of serum. The left radius and ulna were fractured and a plaster bandage applied.

March 12: The animal had not completely recovered from the anesthesia. There was not any evidence of tetany.

March 13: The bandage was removed. The cat took food.

Figure 13

Figure 14

Fig. 13 (series III, cat A).—Forty-nine days after fracture. The arrow indicates callus.

Fig. 14 (series III, cat B).—Forty-nine days after fracture. The arrow indicates callus.

March 14: The general health was good. The blood calcium was 10.7 mg. per hundred cubic centimeters of serum. The animal did not put her injured leg to the ground.

March 17: The animal held the injured leg off the floor when walking.

March 22: She walked with a limp; and on palpation of the fracture a certain amount of thickening was perceptible, although slight angulation at the site of the injury could be obtained if pressure was applied to the lower fragment.

March 30: The cat walked with a barely perceptible limp. A roentgenogram showed a definite deposit of callus. There was firm bony union, as tested by handling.

April 5: The union was solid and the animal moved about without any disability.

Cat 101.—March 8: An adult cat, with a blood calcium of 11 mg. per hundred cubic centimeters of serum was used. Both parathyroids were removed from the right side and one parathyroid was removed from the left side. The left radius and ulna were fractured. A plaster bandage was applied.

March 9: The animal had not completely recovered from the anesthetic. The blood calcium was 9.8 mg. per hundred cubic centimeters of serum.

March 10: The animal completely recovered from the anesthesia. There was no tetany. She took food.

March 17: The cat walked on three legs. There was no evidence of bony union, as tested by handling. The blood calcium was 9 mg. per hundred cubic centimeters of serum.

Figure 15

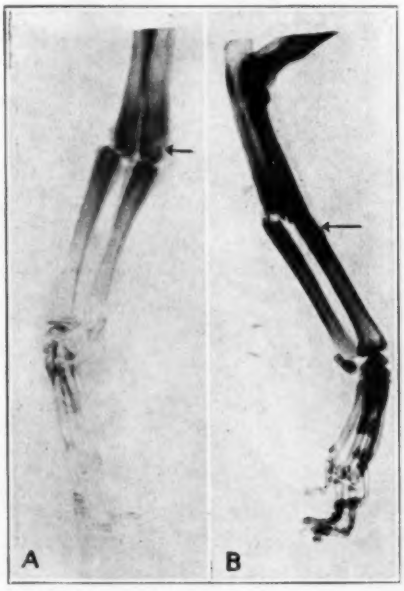

Figure 16

Fig. 15 (series III, cat C).—Forty-nine days after fracture.

Fig. 16 (series IV, cat A and B).—*A* shows cat C twenty days after fracture. The arrow indicates a callus. *B* shows cat B twenty days after fracture. The arrow indicates a suggestion of callus.

March 22: The general health was excellent. The animal did not put her foot to the floor when walking.

March 25: Pressure applied to the lower fragment produced angulation at the site of the fracture.

March 31: The animal did not attempt to apply her injured leg to the floor when walking. She was killed on this date.

Gross examination of the fracture showed that there was a tough membrane encircling both ends of the fragments, and while this mem-

brane (with all the muscles removed) allowed of lateral movement at the site of the fracture, it did not allow any extension unless it was torn across by the force of the pull. It was easily cut through with a scalpel and did not offer any hard resistance. Sections were taken for microscopical examination, and these did not require to be decalcified previous to cutting with the section knife.

Blood phosphate determinations both before and after the removal of either two or three parathyroids did not reveal any change in the blood phosphate level.

In addition to the four series of experiments described, other less complete series were carried out. These latter, complicated by failure to effect clean removal of the parathyroid glands or by other misadventure,

Fig. 17 (series IV, cat A).—Thirty-eight days after fracture. The arrow indicates callus.

have not been considered worthy of detailed description. At the same time it is well to mention that no exception to the foregoing general observations occurred in any single case, and delayed union was present only when three parathyroids had been removed.

The results obtained from these experiments, as exemplified by the accompanying histories, show that if two parathyroids are removed either from the same side or one from each side, there is no delay in the time of deposition of callus at the site of fracture as compared with the control animal. In the animals in which three parathyroids are removed there is little, if any, deposit of callus (as determined by

roentgen-ray examination) until the fifth or sixth week. Further, the age of the animal did not have any apparent effect on the time required for the deposition of callus. The formation of callus appears to depend largely on the amount of the blood calcium. The blood calcium was reduced in these animals by from 2 to 3 mg. per hundred cubic centimeters of serum, and remained at the reduced levels for from four to five weeks. With the return to normal blood calcium there was abundant deposition of callus, and union occurred in the usual manner.

In cases in which only two parathyroids were removed there was not any decrease in the blood calcium value and consequently no delay in bony union.

Complete immobilization of the fractures was not maintained for more than forty-eight hours, yet callus appeared within from fifteen to sixteen days in the normal animals, and union was apparently firm inside of twenty-one days. The alignment of the fragments, as shown by the roentgenograms, was excellent. This would seem to indicate that a certain amount of mobility of the fragments is not at all a hindrance to the formation of callus, and with the care of the injured leg left to the devices of the animal, apposition is maintained.

In the first five to six days following a fracture in a normal animal one sees an invasion of the blood-clot formed at the site of the fracture by fibrous connective tissue. By the tenth to eleventh day the blood-clot has either entirely or almost entirely disappeared and has been replaced by connective tissue, with probably a small amount of cartilage and here and there small areas of new bone. This invasion of the blood-clot by connective tissue and the formation of cartilage occur in cats in which three parathyroids have been removed. The process of repair, however, from then on is delayed, as is shown by the microscopic section of the membrane which is laid down at the site of the fracture in cat 101. Here are seen well organized connective tissue, many new blood-vessels, and small areas of cartilage. This corresponds closely with the picture in a normal animal at about the tenth or twelfth day, with the exception that in the latter new bone formation is generally visible, and callus can be made out by roentgen-ray examination by the fourteenth day. If cat 101 had been allowed to live the blood calcium would have returned to normal about the fourth or fifth week following the fracture; calcium salts would then have been deposited in the connective tissue at the site of the fracture, and union would have occurred in the usual manner.

CONCLUSIONS

1. The removal of two parathyroids does not delay the union of fractures.

2. The removal of three parathyroids delays bony union for as long as from four to five weeks.

3. The excision of two parathyroids does not diminish the blood calcium level, while the excision of three parathyroids causes a drop of from 2 to 3 mg. of calcium per hundred cubic centimeters of serum.

4. When the blood calcium returns to normal level bony union of the fracture occurs.

5. The removal of two or three parathyroids does not influence the blood phosphate level.

6. A certain amount of mobility at the site of the fracture is not deleterious to bony union.

END-RESULT IN THIERSCH GRAFT

A CASE OBSERVED AFTER THIRTY YEARS *

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Since skin grafting, a heritage from antiquity,[1] was placed on a firm scientific basis by Reverdin [2] and later by Thiersch [3] and by Ollier,[4] numerous observations have been made on the phenomena involved in its successful conclusion. Davis and Traut [5] have recently summarized and continued the work begun by Garre,[6] in which the processes of vascularization and innervation of the transplanted tissue have been quite definitely determined. Most of these studies were performed on laboratory animals after varying periods of time, up to two years, had elapsed since grafting. The purpose of this article is not to deal with the physiologic changes involved in transplantation, but to discuss the end-result obtained. This, to be ideal, must closely approach the normal uninjured skin in appearance and function. An opportunity for such a study was presented by a patient who had been operated on thirty years previously by Dr. J. L. Campbell.

REPORT OF A CASE

J. W., a mulatto laundress, aged 20, was treated at the Grady Hospital in 1897 for a varicose ulcer of the left leg. The affected veins were ligated and resected, and the ulcer bed was covered with Thiersch grafts. Convalescence was uneventful, and two months later she resumed her occupation. There was no recurrence of the ulcer, but the foot would occasionally swell slightly after she had been standing for long periods of time. For the past few years this had been more troublesome, but it had only occasionally necessitated the use of an elastic stocking. In April, 1927, nearly thirty years after the grafts were applied, the patient was readmitted to the hospital; she was found to be suffering from a squamous cell carcinoma of the urethra.

At this time, an examination of the leg revealed several small scars over the courses of the greater and lesser saphenous veins and a lightly pigmented area

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* From the Emory University School of Medicine Division of Grady Hospital.

1. Baas: History of Medicine, New York, 1889, p. 46. Davis: Plastic Surgery, ed. 1, Philadelphia, P. Blakiston's Son & Company, 1919, vol. 1, p. 3. Garrison: History of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 64.
2. Reverdin: Bull. de la Soc. de Imp. Chir., 1869, p. 493.
3. Thiersch: Verhandl. d. deutsch. Gesellsch. f. Chir. **3**:69, 1874.
4. Ollier: Bull. Acad. de méd., Paris, 1872, 2s, p. 244.
5. Davis and Traut: Ann. Surg. **82**:871, 1925.
6. Garre, quoted by Davis and Traut: Beitr. zur klin. Chir. **4**:625, 1889.

on the anterior surface of the thigh from which the grafts had been taken. The grafted area (fig. 1) on the lower posterolateral surface of the leg was irregular in outline and about 4 by 8 cm. in area. The grafted skin was fairly movable over the underlying tissue and was thrown into numerous fine folds or wrinkles. The depression of the surface was almost negligible, but there was an easily detected lack of moisture. Some portions of the graft were lighter, while others were more deeply pigmented than the surrounding skin. Sensation to temperature, pain and deep pressure was only slightly diminished, but sensitiveness to light touch was considerably impaired.

Fig. 1.—Appearance of the leg thirty years after grafting by the method of Thiersch.

The urethral growth was well advanced on her admission to the hospital, and radium therapy influenced it but little. When it became evident that the patient would be confined to bed for the remainder of her days, she readily consented to a removal of sections from the grafted areas, from the area from which the graft was taken and from the normal skin of the opposite leg. The specimens were excised with a sharp knife and the edges of the wounds closed. Primary healing occurred, and the patient was none the worse for the procedure. The sections were fixed, mounted and stained by the usual methods and a study made of each.

COMMENT

The normal skin (fig. 2 *C*) showed the usual histologic structure, which needs no description here, but which is useful in a comparative study of the other sections.

The section of transplanted skin (fig. 2 *A*) showed many variations from the normal. There was an excessive conification, the diameter of which equaled that of the stratum mucosum. The intervening stratum lucidum and stratum granulosum were sharply defined. The diameter of the stratum mucosum was much less than that of normal skin, largely owing to the fact that the stratum germinativum was smooth and straight instead of dipping in between the papillae of the corium. The individual cells of the germinal layer stained deeply and were closely spaced. There were no hair follicles, and only rarely a group of cells occurred which

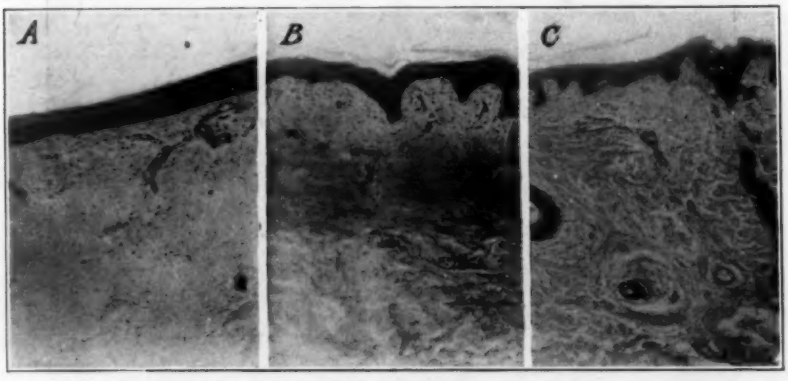

Fig. 2.—Histologic appearance of sections of *A*, Thiersch graft; *B*, area from which the graft was taken; *C*, normal skin of the opposite leg.

suggested the atrophic remains of a glandular structure. The amount of connective tissue was excessive and almost completely replaced the other components of the corium.

The section of skin removed from the area from which the graft was taken (fig. 2 *B*) revealed a structure which in some ways suggested an intermediate state between the normal skin, on one hand, and the grafted skin, on the other. The stratum corneum, while not so pronounced as in the graft, was definitely thicker than is usually found in this region. The stratum germinativum was not smooth and straight, but it did not dip as deeply into the corium as in the normal skin. Well developed hair follicles and glands were found, but there were also atrophic structures which undoubtedly represented such organs injured as the graft was excised at operation.

When the structure of the Thiersch graft is considered, some of these observations can readily be explained. As only the tops of the

papillae corium were supposed to be cut across in the classic thin graft, there would be little undulation of the stratum germinativum when its continuity was reestablished by a lateral extension from the basal cells over the apexes of these papillae. The depth of the papillae was diminished by the operation, and this accounts for the shallowness of the rete pegs in the area from which the graft was taken. The fact that an attempt was made to include as little of the corium as possible explains the absence of glands and follicles in the graft. Unintentional injury to the corium would produce atrophic changes in some of the structures in the area from which the graft was removed. The varying diameter of the stratum corneum in the three sections was directly proportional to the supply of glands and the relative degree of moisture.

SUMMARY AND CONCLUSIONS

After a period of thirty years, a Thiersch graft on the posterolateral surface of the leg of a laundress was found to give excellent protection and a fair cosmetic result. Sensation was only moderately impaired, but secretion and excretion were entirely lost, and for this function the graft was entirely dependent on the adjacent skin. A histologic study disclosed results which were in keeping with the amount of tissue transplanted and the processes involved in its successful conclusion. It would seem that a whole thickness graft would be the method of choice in most instances, because more structures of the corium would persist and thus permit the function of the transplant more closely to approximate the normal.

24 Doctors' Building.

THE HEALING OF FRACTURES

AN EXPERIMENTAL STUDY *

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Some years ago I published the results of an experimental study on the healing of fractures in cats.[1] Three sets of experiments were performed: simple fractures, incision of the periosteum with instrumental division of the bone, and circular division of the periosteum with instrumental division of the bone. As a result of this work, I came to the following conclusions:

1. When the periosteum is intact, bony union is to be expected.
2. When the periosteum is completely divided, bony union is not to be expected.
3. When the periosteum is slit, bony union may or may not take place.

After an ordinary fracture, hemorrhage takes place from the marrow canal under the periosteum. The periosteum is stripped up from the cortex by this hemorrhage and by the fracture itself. Then come the deposition of fibrin, the formation of granulation tissue and the formation of cartilage and fibrocartilage in the space beneath the stripped up periosteum. Probably the function of the periosteum is important only in the early stages, up to the formation of the cartilaginous callus. The periosteum probably serves to keep the hemorrhage from escaping and the granulation tissue undisturbed. It has no bone-forming function, and bone is not built of it. The subsequent ossification of the cartilaginous callus is carried out almost entirely, if not exclusively, from the external aspect of the cortex. The internal callus does not play an effective part in the union. It is rudimentary when it is present.

The present study was undertaken in order to investigate farther the rôle of the periosteum in the healing of fractures. I proposed to remove the periosteum circularly from an appreciable length of bone, and then to fracture the bone. If, after this was done, union took place, the so-called bone-forming function of the periosteum could be discounted. I found that such an operation is extremely difficult, if not actually impossible. In some operations I removed as much of the periosteum as possible from about 1.5 cm. of the humerus, before fracture; in others, I contented myself with simply stripping the periosteum from about 7 mm. of the end of each fragment.

The wound was then closed, and a collodion dressing was applied. Cats were chosen for the experiment, and the operations were performed under complete ether narcosis, and with asepsis. I operated on ten cats. Five of these died within a few days, and are omitted from

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* From the Laboratory of Surgical Research, Stanford University.

1. Ely, Leonard W.: Arch. Surg. **5**:527 (Nov.) 1922.

consideration. The others died or were killed at intervals. The humerus, with the surrounding soft tissues, was removed and placed in a solution of formaldehyde, and then in alcohol. It was decalcified in 5 per cent nitric acid, run up through alcohol, dehydrated with ether, mounted in celloidin and stained with hematoxylin and eosin and with the van Gieson stains.

EXPERIMENTS

CAT 46.—Duration of experiment, thirty-two days.

Operation.—The incision was made posterior to the deltoid muscle and the long head of the triceps down to the humerus. As much of the periosteum was removed as was possible for a distance of about a centimeter. The humerus was divided with Liston forceps, and the periosteum was scraped for a distance of about 7 mm. from the end of each fragment. The wound was closed with deep chromic and superficial plain catgut. Collodion dressing was applied.

The animal was found dead thirty-two days later. The wound had healed by first intention, and signs of infection were not present. The fragments were freely movable, and much deformity was present with overlapping.

Microscopic Study.—The fragments overlapped about 2 cm., and did not lie closely together. They had been caught somewhat on the bias by the knife, so that it was necessary to study two slides to get the exact facts. The end of each fragment had been shut off by fibrous tissue, which stretched across the open marrow canal in irregular bundles and ran for a short distance down into it. Irregular bone trabeculae were scattered in the marrow canal of each fragment, but it was impossible to tell whether or not these were newly formed. The periosteum could be traced almost to the end of the inside cortex (that is, the cortex on the side adjacent to the other fragment) of one fragment and to the end of the outside cortex of the other fragment. In the latter, it was continuous with the fibrous tissue plugging up the marrow canal. Each bone showed a subperiosteal callus near the end of its outside cortex. The cortices of both fragments had a rather openwork structure near their ends, apparently the beginning of the rearrangement of the bony tissue. The space between the two fragments was filled with fibrous tissue and cartilage, but little sign of ossification appeared in this. From the appearance of the slide, it was possible that bony union would have taken place in time.

Result of Experiment.—Thirty-two days after removal of the periosteum, as nearly complete as possible, a false joint was found.

CAT 47.—Duration of experiment, 119 days.

Operation.—An incision was made like that in cat 46, and the same type of operation was performed except that the periosteum was separated from about 7 mm. of the end of each fragment, and little of the periosteum was actually removed.

When the cat was killed, he was able to walk on the leg without a limp. The fracture apparently was united, with considerable overriding.

Microscopic Study.—The two fragments were firmly united by bone. The bony callus had reached such a state of development that it was fairly dense at its periphery, and spongy within. The cancellous bone possessed marrow with the same appearance as that within the marrow canals of the fragments themselves. Rearrangement of the bone had proceeded so that the distinct outline of the fragments was difficult to make out, but apparently one had been caught on the

bias. The marrow canal of the other fragment was continuous with the marrow in the new callus, and the dividing line between them was difficult to make out. The extreme end of the cortex of the closed fragment was irregular in its contour, with indentations like Howship's lacunae. Dead bone could not be seen.

Result of Experiment.—Bony union occurred 119 days after the fracture, with removal of little periosteum, but with stripping of the periosteum from about 7 mm. of the end of each fragment.

CAT 48.—Duration of experiment, thirty-three days.

Operation.—The incision was made between the triceps and the deltoid. The periosteum was separated from about 7 mm. of the end of each fragment, but little of it was removed.

Figure 1

Figure 2

Fig. 1 (cat 46).—Photograph of the stained slide. Note the mass of cartilaginous callus and fibrocartilaginous callus between the two adjacent cortices. One of the fragments is caught on the bias, the other is caught square.

Fig. 2 (cat 46).—Photograph of another slide showing the other fragment caught square by the knife. It is likely that this experiment would have ended in bony union.

When the cat died from an unknown cause there were no signs of infection. Overriding of the fragments was present, but apparently union had begun, for motion was restricted at the site of the break.

Microscopic Examination.—Both fragments were caught by the knife on the bias, and the ends of the marrow canals were therefore shut off by the cortex. In the marrow canal of each fragment new bone trabeculae had been developed apparently from fibrous tissue, but there was no evidence that this new bone was

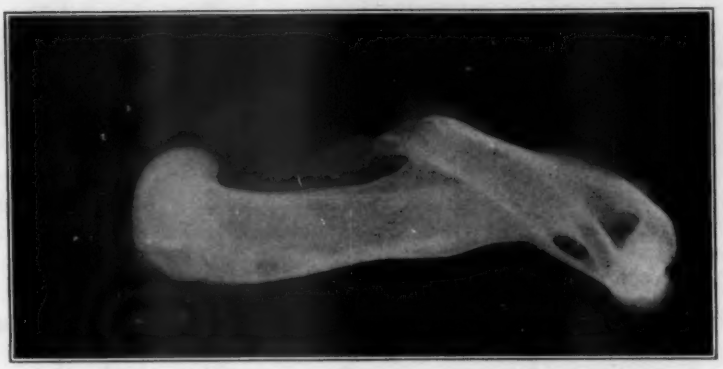

Fig. 3 (cat 47).—Roentgenogram of the specimen.

Fig. 4 (cat 47).—Bony union. A new cortex has already formed about the bony callus. If this were an isolated experiment one might claim that the cortex had been formed by the periosteum. Note the partially completed absorption of the adjacent cortices.

playing an active part in the process of healing. In one fragment the cortex was being broken up as if for rearrangement of its structure. The two fragments overrode 1.5 cm. and their cortices were not contiguous. There was a space of almost 1 cm. between them which was bounded on two sides by bone and on two sides by irregular bundles of fibrous tissue. It was almost filled by two masses of cartilage, one on each cortex, and between these two masses of cartilage there was a distinct space like a joint cavity. It appeared as if the cartilage were being formed from fibrous tissue, for fibrous tissue still ran in between the two masses and shaded into their structure. Ossification of this cartilaginous callus had begun from the cortex. There was no evidence of any bony bridge in the periosteum, nor, in fact, did any distinct periosteum stretch across the gap between the two fragments. The entire cortex was alive. There was no dead bone anywhere.

Result of Experiment.—A fairly stable false joint was found thirty-three days after fracture, with separation of the periosteum from the cortex of each fragment for a distance of 7 mm. A free production of cartilaginous and bony callus had

Fig. 5 (cat 48).—Roentgenogram of the specimen.

been made on each fragment, but these were separated by what had every appearance of being a joint.

Cat 50.—Duration of experiment, twenty-five days.

Operation.—The periosteum was removed where it could be easily reached. The bone was divided, and the periosteum was separated from each fragment for a distance of about 7 mm. from its end. The wound healed by first intention. When the cat died the fragments of the humerus moved freely on each other, with marked overriding.

Microscopic Examination.—The fragments overlapped to the extent of about 1.5 cm., and there was a space between them of about 6 mm. The cat was young, as the epiphyseal cartilage disk was still present. The open marrow canal of one fragment was plugged with fibrin showing areas of calcification in its meshes. This fibrin was fairly sharply defined from the marrow tissue, but in some places shaded into the fibrous tissue of the marrow. The open end of the other fragment was plugged with fibrous tissue. The divided ends of the cortex had been very much splintered, and besides this, they were being opened longitudinally in slits. Blood vessels could be seen in some of these slits. There was no evidence

of any bone formation at the end of the open marrow canal. On the outside of one cortex there was a large fragment of bone which was evidently splintered off at the time of the operation, and which had worked its way down along the side of the cortex. On the far cortex of one fragment a rather long strip of new bone formation could be seen under the periosteum. This new bone ceased at some distance from the end of the fragment fairly abruptly and did not appear to be playing any useful part in the healing process. It seemed to be developing from fibrocartilage, and for some distance from the place where it ended, the gap between the cortex and the periosteum was filled with cartilage and fibrous tissue. On the cortex of this fragment, facing the other fragment, but at some distance from the end, was a sort of semicircular collection of fibrin and fibrous tissue,

Figure 6

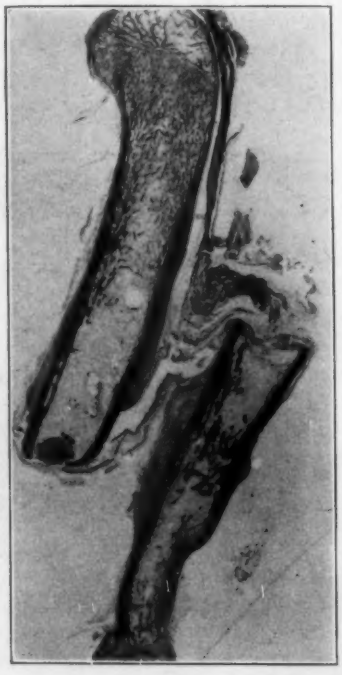

Figure 7

Fig. 6 (cat 48).—Nonunion. Note the irregular masses of new cartilaginous callus on the adjacent cortices with a distinct cleft between them. This specimen illustrates all the elements of a false joint.

Fig. 7 (cat 50).—False joint. Note the new bony and cartilaginous callus on one of the adjacent cortices.

and on this near cortex a few new bone trabeculae had been formed. On the corresponding cortex of the other fragment there was a large mass of cartilage and fibrocartilage in which new bone formation had been active. On the far cortex of this fragment, but nowhere near its end, a few new trabeculae had been formed. New bone trabeculae in the form of an internal callus were also in evidence in this fragment, but in irregular formation. The two fragments were separated by fibrous tissue loosely arranged and with long slits in it, and the

surface of the fibrous tissue bordering on these slits had much the appearance of a synovial membrane. In the open spaces were collections of fibrin. The whole appearance of the tissues was that of a forming joint. It was improbable that union ever would take place, no matter how long the animal had lived.

Result of Experiment.—Twenty-five days after fracture, with removal of some periosteum from the end of the fragments, and with a denudation of the cortex for 7 mm., a new joint was evidently forming.

CAT 52.—Duration of experiment, seventy-six days.

Operation.—An incision was made between the deltoid and triceps as in the other operations. Great care was taken to remove as much of the periosteum as possible from about 1 cm. of the shaft of the humerus, and little of the periosteum was stripped back. When the cat died, union had apparently taken place with much overriding.

Microscopic Examination.—The stained slide did not show nearly as much overriding as appeared in the gross specimen. The end of one fragment had been caught on the bias by the knife so that the cortex closed it. The end of

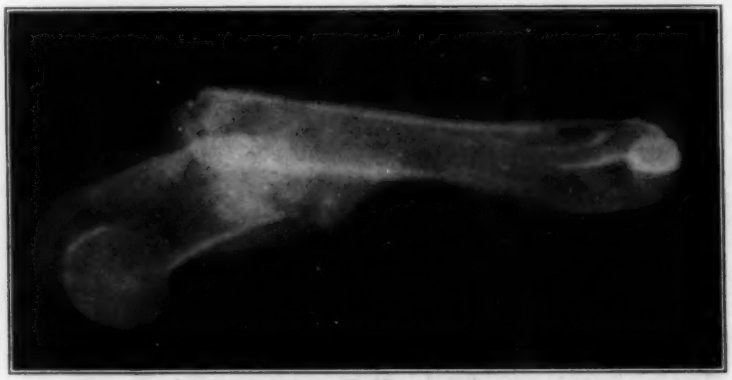

Fig. 8 (cat 52).—Roentgenogram of the specimen.

the other fragment had been caught square. The two fragments were firmly united by bone, and the catching of one fragment on the bias enabled one to see very well the extent of the bony callus. New bone trabeculae in the shape of fairly loose-meshed spongy bone had formed in the open end of one fragment, partially blocking it, and these were separated from the rest of the bony callus by a mass of fibrous tissue, fibrocartilage and hyaline cartilage, which was evidently undergoing ossification, with new bone trabeculae springing from the cortex of the closed fragment. In fact, the most active bone formation appeared to be taking place from the outside of the cortex. Across most of one side of the callus the periosteum could be traced, and underneath it and springing from the closed cortex of the fragment a new cortex was forming for about one-half the distance across the gap. The other side of the callus was irregular, and a continuous periosteum could not be traced across it. New bone production was, as usual, free in the angle where the periosteum leaves the bone. On the outside of the far cortex of the open fragment, the periosteum had not re-formed at the end of the bone from which it was stripped at the time of the operation, but at a considerable distance from the fractured end of the bone a strip of new trabeculae

was forming on the outside of the new cortex under the periosteum. This new bone appeared to be formed from the cortex out of cartilage and fibrocartilage. Dead bone could not be recognized in the slide, and there was no evidence of rearrangement of the bone tissue of the cortex, nor of any osteoclasis, that is, osteoclasts in Howship's lacunae could not be seen.

Result of Experiment.—A firm bony union resulted after seventy-six days, through the medium of cartilage and fibrous tissue after removal of as much of the periosteum as possible without stripping it back. Bone formation apparently occurred from the cortex. There was no periosteal bridge, though at one area a new cortex had partially formed under the periosteum for a certain distance out from the old cortex. There was no evidence of internal callus.

Fig. 9 (cat 52).—Union by intracartilaginous ossification. The fragment which has been caught on the bias with the knife shows well the many new trabeculae apparently springing from the cortex. In the other fragment the trabeculae extend into the marrow canal.

SUMMARY

The following results were obtained from experiments on five cats: one fracture with removal of periosteum, 32 days, cartilaginous union; one fracture with stripping of periosteum, 119 days, union; one fracture with stripping of periosteum, 33 days, no union; one fracture with removal of periosteum, 25 days, no union, and one fracture with removal of periosteum, 76 days, union.

The two cats that were allowed to live more than thirty-five days showed bony union. In one of them the periosteum had been removed as carefully as possible; in the other it had simply been stripped. In the three animals killed in less than thirty-five days, bony union was not present. In two of these the slides looked as if a new joint were being formed, but it was difficult to be sure.

Apparently, though the experiments are too few to determine this, the result of stripping the periosteum is the same as of removing it.

Most of the activity in new bone formation after fracture with overriding is on the outside of the two cortices facing each other. In this bone formation the periosteum does not take part. The internal or medullary callus does not play an active part.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 806)

URETER

Ureterostomy.—Papin [29] described a method of anterior ureterostomy for exclusion of tuberculous bladder. The lower end of the ureter was freely liberated, sectioned close to the bladder and brought out through the skin near the anterior-superior iliac spine. The ureteral curve should be long in order to avoid kinking. A cutaneomucous suture is not made, but a portion of the ureter is left protruding above the skin; the portion later sloughs off. A ureteral catheter is left in place until complete cicatrization occurs; it should be closely observed and changed if necessary. In one case, Papin put the ureter in a small pocket made of skin, but it was unsatisfactory as considerable scarring occurred. This type of ureterostomy has been performed from one month to twelve years after nephrectomy, and the operation has not caused any deaths. The vesical pain is immediately and completely relieved, and the anterior site of the operation renders it more bearable than the lumbar site.

Ureteral Stones.—Cope [30] reported a case of large ureteric calculus. The patient was a lad on whom left nephrectomy had been performed a year previously for pyonephrosis. He complained of continuous pain on that side. A roentgenogram revealed the calculus, which was about 4 by 2 by 1 cm., in the lower end of the ureter; it was probably overlooked at the previous operation. The stone and ureter were removed.

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29. Papin: Urétérostomie sur le rein restant, après néphrectomie pour tuberculose vésicale, Presse méd. **35**:854, 1927.

30. Cope, V. Z.: Large Ureteric Calculus, Proc. Roy. Soc. Med., Sect. Urol. **20**:16, 1927.

[ED. NOTE.—It is not necessary to remove all ureteral stones in performing nephrectomy and partial ureterectomy. If the ureter is not dilated or markedly infected, small, partially obstructing stones in the lower part of the ureter do not cause trouble. Complete nephro-ureterectomy is a much more extensive procedure than simple nephrectomy and adds greatly to the operative risk. Dilated ureters containing large stones should be removed at the time of the nephrectomy if the patient is in good condition, or they may be removed later if they cause pain or urinary infection.

Large ureteral stones are only rarely seen in this period of accurate urologic diagnosis. In 1909, Federoff [31] reported a case in which the stone weighed 52 Gm. In 1910, Porter [32] reported a case in which the stone weighed 95 Gm. Israël [33] removed a ureteral calculus 17 by 2 cm.]

Rathbun [34] reported a case of bilateral diverticula of the ureter. The patient, a boy, aged 10, complained of dysuria and frequency. The urine was highly infected, and cystoscopy revealed general diffuse cystitis. A roentgenogram after ureteral catheterization showed the catheters on both sides coiled up in a diverticulum. At operation, a somewhat enlarged and much thickened bladder was fully exposed and freely mobilized through an extraperitoneal, median incision extending from symphysis to umbilicus. The diverticula were found in the depths of the wound buried in a mass of adhesions, particularly on the right side where the diverticulum was with difficulty dissected free from the seminal vesicle. The sac apparently consisted of the lower end of the ureter communicating with the bladder through a tiny opening at the normal site of the proximal end of the intramural portion and above with moderately dilated and much thickened ureters. The sacs and about 4 cm. of the ureter immediately above were excised, and the bladder openings closed with a single chromic suture. The bladder was opened through a slit made near the summit. The ureters were reimplanted fairly high in the posterior wall. A Pezzer catheter was anchored in the bladder, rather free prevesical and perivesical drainage were established and the usual closure made around the drains. The diverticular sacs were lined with transitional epithelium continuous with, and of the same type as, the epithelium lining of the ureter itself,

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31. Federoff, S. P.: Zur Kasuistik der Ureterstein, Ztschr. f. Urol. **3**:65, 1909.

32. Porter, M. F.: Kidney and Ureteral Stones, J. A. M. A. **55**:1691 (Nov. 12) 1910.

33. Israël, quoted by Pappa, A.: Contribution a l'étude des calculs de l'uretère, Ann. d. mal. d. Org. Gen.Urin. **26**:1694, 1908.

34. Rathbun, N. P.: Bilateral Diverticula of the Ureter, J. Urol. **18**:347, 1927.

which showed numerous small hemorrhagic areas and several small superficial ulcerations. There was definite evidence of inflammatory reaction throughout, and marked hypertrophy of the musculature, both of the wall of the sac and of the ureter.

The patient recovered uneventfully and the wound healed readily. He looks and feels much better. He urinates only once at night and the intervals during the day are as long as three or four hours. There is no dysuria, and while the urine still contains abundant pus, it is much clearer than before operation. As both kidneys were undoubtedly affected, Rathbun does not believe that the immediate improvement will be sustained.

BLADDER

Vesical Stone.—McCarrison [35] reported a series of experiments on the production of stone in the bladder. One hundred twenty rats were placed on a diet in which there was: (1) absence of protein of animal origin, (2) deficiency of vitamin A and (3) excess of earthy phosphates. To these faults there may have been added toxic action of the diet itself in the urinary tract.

Formation of stones did not occur in rats kept on the diet for a period less than fifty-six days. Twenty-one (seventeen females and four males) of the seventy-two animals kept on this diet for longer than fifty-six days, were found at postmortem examination to have stone in the bladder; the case incidence was 29 per cent. The incidence of the disease varied in the two sexes, being 40 per cent in females and 13 per cent in males. In two other cases in females intense cystitis, but no stones, was present, in one of these there was some earthy incrustation around the neck of the bladder. Hemorrhage from the bladder was occasionally observed during life. In males, protrusion of the penis was a constant symptom in those suffering from stone.

In eighteen cases in which a stone was found, a greater or lesser degree of cystitis was present; in these, the bladder was usually greatly distended and congested. In three cases, cystitis did not occur, showing that the deposition of the phosphatic calculi was not secondary to inflammation of the bladder. In eight cases, the left ureter was much dilated, with associated pyonephrosis or hydronephrosis. Earthy deposits were present in the kidney in four cases, but stones did not form. The stones in the bladder were either single or multiple, as many as five being found in one bladder; they were dirty white, and their surfaces were rough and jagged. Formed stones were not found, or if found, they were so small as to be more properly called gravel.

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35. McCarrison, Robert: The Experimental Production of Stone in the Bladder, Brit. M. J. 1:717, 1927.

Earthy incrustations around the neck of the bladder were sometimes present. The stone, stones or gravel varied in weight in individual cases from 17 to 27 mg. in males and from 8 to 35 mg. in females. The largest single stone weighed 35 mg.; a stone of proportionate size in man would have weighed about 0.5 Kg. Chemical examination showed the calculi to consist mainly of earthy phosphates (calcium and magnesium) along with traces of calcium oxalate. Stone was found only in animals that died between the eighty-fourth and the one hundred and fifty-seventh day of the experiment; the onset of the disease did not appear until fifty-six days after the initiation of the diet.

During the 157 days this experiment lasted, 340 postmortem examinations were made on rats that had been fed in various other ways. In none of these was stone present in the bladder.

Bikovtseva [36] stated that vesical calculi are most common during childhood; they are rare in middle age and again more common after the age of 40. They are much more common in males than in females. Most stones can be removed through the urethra or by crushing. If these procedures are not successful in women, colpocystotomy can be performed.

Diverticulum.—Davis [37] reported a case in which a large diverticulum of the bladder was drained suprapubically. Later the diverticulum was resected by an ingenious method; a Young prostatic retractor was inserted in the sinus and traction put on the diverticular sac which permitted it to be dissected free. The prostate was also removed, following which further urinary difficulty did not occur.

[Ed. Note.—The diverticulum in this case was very large. Small diverticula are generally rounded or oval, and lie between the bladder and rectum extending laterally and upward as they increase in size. It is usually only very large diverticula that come to lie above the bladder. In about 30 per cent of cases, it is necessary to perform prostatectomy as well as to excise the diverticulum. Usually if the multiple stage operation is carried out, these two procedures give good results and are attended by a comparatively low mortality rate.]

Kaufer [38] noted that diverticula of the bladder are common and are usually concerned with urinary obstruction, increased intravesical pressure and lowered resistance of the wall of the bladder. They occur as bulgings of mucous membrane through the muscle bundles. Kaufer

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36. Bikovtseva, M. J.: Blasensteine bei Frauen, Meditsin Obozr. Nizhn. Povolzhya Astrachan, 1926; obstr. Ztschr. f. Urol. **21**:475, 1927.

37. Davis, D. M.: Preliminary Diverticulostomy in Diverticulum of Bladder; Unusual Case and Method of Operation, J. A. M. A. **89**:192 (July 16) 1927.

38. Kaufer, L.: Ueber ein ungewöhnlich grosses Blasendivertikel, Ztschr. f. Urol. **21**:430, 1927.

cited a case in a man, aged 76, with marked kyphosis and scoliosis, arteriosclerosis, apoplexy and hemiplegia. At necropsy, on opening the abdomen, a large pelvic cystic mass about 15 cm. in diameter was found. The kidneys were small. This cystic mass was connected with the bladder. The bladder was markedly dilated, the walls were thickened and hypertrophied and showed coarse trabeculations and cellule formation. The urine was under great pressure. About 3,000 cc. was taken from the bladder and diverticulum. The prostate showed hypertrophy of both lateral lobes, while the middle lobe was about 1 cm. in diameter and acted as a valvular obstruction. The diverticulum was 18 by 9.5 by 17.5 cm.; its orifice was 3 by 2.5 cm. Histologic examination of the diverticular wall showed an absence of mucous membrane and an increase in connective tissue. In some areas, muscle fibers were found; these were thinner in the dome than in the posterior wall. Kaufer stated that this diverticulum did not cause any symptoms. He differentiated what is termed true diverticulum from false diverticulum. The former contains all the constituents of the wall of the bladder while the latter does not. In this case there were some muscle fibers in the wall of the diverticulum, although in small quantities, and therefore Kaufer considered it true diverticulum. After reviewing the literature, he believed that the diverticulum in his case is the largest true diverticulum on record.

[Ed. Note.—Large vesical diverticula sometimes do not cause trouble. They are found at necropsy in old men who have died from other diseases, and who have had little, if any, vesical trouble during life. Apparently as long as the wall of the diverticulum is capable of contracting regularly and emptying its contents, and is not infected, it is a harmless condition. Obstruction of the bladder, retention of urine, infection and the not uncommon sequelae (formation of stone or malignant degeneration) make this abnormality serious, and sometimes rapidly fatal. Harrison [39] reported a case of a man, aged 103, who died suddenly from acute pericystitis which developed following infection of an apparently quiescent vesical diverticulum.

Diverticula vary in capacity from about 1 cc. to several liters. While Kaufer's case was unusual, diverticula as large or larger than the normal bladder are not uncommon. Israël [40] recorded the case of a man, aged 66, with a diverticulum three times the size of the bladder.

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39. Harrison, R.: Saccules and Pouches of the Urinary Bladder, Internat. Clin. **3**:243, 1894.

40. Israël, J.: Bericht über die chirurgische Abtheilung des jüdischen Krankenhauses zu Berlin, für den Zeitraum vom 1. Januar, 1873, bis. 1. October, 1875, Arch. f. klin. Chir. **20**:1, 1877.

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Targett [41] cited Green's case, in which the diverticulum held about 4 liters of urine. Potherat [42] reported a case in which a sac held 5.5 liters.]

Tumors.—Wade [43] stated that the majority of vesical tumors cause symptoms at an early stage. Casper used the cystoscope in 142 cases of tumor of the bladder immediately after the first attack of hematuria; all but three were small early tumors.

Vesical tumors with papilliform ingrowths are of three varieties: innocent, transitional and primarily malignant. The first is the innocent, villous papilloma. The second is the malignant papilloma which appears always to evolve after a longer or shorter interval out of the innocent villous papilloma. The third is primary papillary carcinoma.

The appearance presented by a benign villous papilloma of the bladder may be compared to an oak tree. Sometimes it is viewed from above, sometimes from the side. In the latter case its well proportioned stem is seen beneath the overhanging branches of the growth. To view this stem, however, it is sometimes necessary to push aside the long, low-hanging, waving branches, and as these gently wave in the fluid medium the delicate peripheral leaves proclaim the innocence of the growth. If the area around the base of the growth is seen to be roughened, vascular and granular, this appearance is suggestive of early malignant change. This "brushwood" area is the site from which a recurring crop of young seedlings spring, and ultimately may be the site of a more malignant new growth. If an innocent villous papilloma has undergone malignant change, it is not easy at first to recognize the transformation. Later, however, the appearance is more characteristic. The delicate branched villi become fused into a more uniform mass with a roughened surface. The stem is no longer trunklike; the growth is more sessile. The surrounding area is irregular and granular, and ultimately the surface of the growth may become ulcerated with a gray slough covering one part. Primary papillary carcinoma is sessile, with an irregular, excavated, ulcerating surface. Primary epithelioma of the bladder has the appearance of a malignant ulcer, while adenocarcinoma presents an excavated center with overhanging margins.

The treatment for tumors of the bladder is determined by their nature, size and extent of dissemination. There is only one form of treatment indicated for a benign villous papilloma of moderate size,

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41. Targett, J. H.: Abstract of a Lecture on the Pathology of Cystic Tumours Connected with the Bladder, Brit. M. J. **2**:218, 1893.

42. Potherat, quoted by Gayet, G., and Gaulhier, C.: Les diverticules de la vessie, J. d'urol. méd. et chir. **14**:293, 1922.

43. Wade, Henry: The Treatment of Tumours of the Urinary Bladder, Tr. Med.-Chir. Soc. Edinburgh, 1926-1927, Edinburgh M. J. **34**:1, 1927.

and that is fulguration or destruction by electrical coagulation by a high frequency current carried to it by an electrode conveyed through an operating cystoscope. Wade does not recommend fulguration for primary carcinoma of the bladder. The treatment adopted is determined by the situation and extent of the growth. The most favorable case is that in which the tumor is situated in the summit of the bladder. Tumors in this situation are easily recognized, but it is necessary to make certain that they are not invasions from other organs. Complete excision should be carried out when the growth is primary and on the fundus. If the base of the bladder is involved, it is of the greatest importance to determine the degree of invasion and the extent to which the ureters are implicated. If the prostate in the male is not involved and the growth is reasonably mobile, and one ureter and the bladder around it are free from disease, partial cystectomy may be performed successfully. Half of the bladder may be excised and the ureter on that side implanted into the portion that remains. Wade has had ten such cases, all successful. He stated that the appearance of the bladder at the conclusion of the operation is most unusual; but, if examined some months later, it will be found that nature has successfully restored its shape and contour.

[Ed. Note.—Wade's classification of papillary tumors of the bladder conforms to that generally accepted by most urologists. The present tendency is to include most of these tumors in the malignant group; certain pathologists even consider all papillary tumors of the bladder malignant. Areas of malignancy may usually be found even in the small, apparently benign, tumors. In many areas the cells may retain the regularity of benign papilloma; in others they are undergoing various stages of alteration with marked variation in size, type and staining qualities. Some urologists use the size of the tumor as the basis for the type of treatment to be carried out; usually a papillary growth not more than 2 or 3 cm. in diameter will respond to fulguration.

Grossly, the papillary growths may be divided into the aborescent and the solid tumors; probably many of the solid tumors were previously of the branching, wavy variety. The solid tumors are of two types, widespread papillary epithelioma, and low, flat, infiltrating carcinoma. The former has a rolled-out advancing border, the upper surface often being covered with short, stubby, papillomatous protrusions, or the top may have sloughed off, leaving a flat, ulcerated surface. These tumors are sometimes firm, but are often soft, flabby and friable, and can easily be scraped off from the surface of the bladder. The histologic picture usually shows the relation of this tumor to the papilloma; remnants of the central connective tissue axis of altered papillae are common and occasionally rounded ends of fairly normal villi are seen.

In the filtrating type, the margins slope outward to meet the mucosa and burrow down into the wall of the bladder. These tumors are generally firm and compact, and without a tendency to split in cleavage planes. The only difference in the histology of the solid tumors is that most of the infiltrating tumors show none of the remnants of papilloma commonly seen in papillary carcinoma.]

Leukoplakia.—Hennessey [44] reviewed seventy-nine cases in the literature and one of his own of vesical leukoplakia associated with vesical calculus, right infected hydronephrosis and a severe infection of the urine by *Bacillus coli.* He believed that chronic inflammations, irritations and calculi are important factors in the production of leukoplakia. In the urinary tract, leukoplakia is most commonly found in the bladder. The lesion is more common in the male, the ratio being about 3:1. Pathologic observations indicate a precancerous tendency in the area affected by leukoplakia. Treatment has been variable and uncertain. Fulguration of the vesical lesions has been thought to be beneficial.

[Ed. Note.—Leukoplakia has long been a subject of interest and conjecture because of unknown etiology and pathologic significance. The occurrence of such a process in the urinary tract, reproducing exactly the microscopic and gross appearance of skin, together with its relative rarity, renders any study important which helps to explain the etiology of this unusual condition. The urinary tract is embryologically of entodermal and mesodermal origin, whereas leukoplakia is an epithelial process (ectoderm). The interest in the subject led to an extensive review by Hinman, Kutzmann, and Gibson,[45] whose views and observations have been further substantiated by Hennessey. Leukoplakia has been found usually to be associated with inflammation of long standing, calculus formation or other irritation, which seem to be the usual contributory factors.

The etiology is unknown. The most common theories are: 1. Leukoplakia is a time metaplasia on the basis of chronic inflammation and irritation, or the biologic process of adaptation to environment in the form of protective cornification. 2. Leukoplakia of the urinary tract arises on the basis of misplaced embryonal rests of primitive ectoderm.

The symptoms are those of infection of the urinary tract (cystitis, pyelitis, pyelonephritis, pyonephrosis) and urinary lithiasis, conditions with which leukoplakia is usually associated. The treatment of choice

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44. Hennessey, R. A.: Leukoplakia of the Bladder, J. A. M. A. **88**:146 (Jan. 15) 1927.

45. Hinman, Frank; Kutzmann, A. A., and Gibson, T. E.: Leucoplakia of the Kidney Pelvis with Reports of Two Cases, Surg. Gynec. Obst. **39**:472, 1924.

is surgical whenever possible since it is incurable and precancerous, having been considered the forerunner of squamous cell carcinoma.]

Rupture of the Bladder.—Negley [46] reported thirty-four cases of rupture of the bladder. Fourteen cases were of extraperitoneal rupture; four patients died, a mortality of 28.6 per cent. Three of the four patients had been operated on two, three and five days, respectively, after injury. The fourth patient was operated on two hours after injury, but death resulted from torn pelvic blood vessels and cannot be attributed either to operation or vesical rupture. Eliminating this death, the mortality is 21.5 per cent. In the first three cases, there were complications; the patient operated on two days after the injury had stricture and gangrenous cystitis; the one operated on three days after the injury had a fractured pelvis, extravasation of urine and pelvic cellulitis, and the one operated on five days after injury had prostatic obstruction and extravasation of urine. The patients recovering after operation had extravasation with cellulitis, stone in the posterior urethra, fractured pelvis, fractured femur, and stricture of the perineal urethra. In the successful cases, the shortest time between injury and operation was four hours and the longest time thirty-two days. The operative procedure included a cystotomy wound in a clean portion of wall of the bladder, closure of the wound if it was clean and easily accessible, and rubber tissue and iodoform cigaret drainage in the prevesical space, making sure that the bottoms of all possible infected cavities were reached by the drains.

There were twenty cases of intraperitoneal rupture; four patients died, a mortality of 20 per cent. These four were operated on within twenty-four hours, two days, two and a half days, and three days, respectively. The complication in the first case was a torn mesentery with hemorrhage; in the second and third cases, the complications were fractured pelvis and shock, and in the fourth case the complication was puncture of the lung from fractured rib. The patients who recovered had the following complications: fractured pelvis, nine; peritonitis, nine; fracture of the femur in the hip joint, three; torn mesentery, three; ruptured intestines, two, and fractured skull, one. Operation included opening of the peritoneal cavity, mopping up or aspirating all the free fluid which was within easy access, rubber tissue drain through the lower angle of peritoneal opening, cystotomy wound in clean portion of bladder, suture of wound only when it was clean and easily accessible and drainage of bladder with a catheter or tube. In the cases in which the patients recovered, the longest time between injury and operation was five days; in all the others it was twenty-four hours or less.

46. Negley, J. C.: Rupture of the Bladder, J. Urol. **18**:307, 1927.

[Ed. Note.—Negley's statistics compare favorably with those reported by other authors. Twenty or thirty years ago, almost all cases of rupture of the bladder were fatal. In 1887, Ullman [47] reported only twenty-two recoveries in 237 cases. Ninety-four of these were extraperitoneal; twenty patients recovered. Only two of 143 patients with intraperitoneal rupture recovered. Bartels [48] reported a mortality of 96 per cent in ninety-eight patients treated without operation. Dobrowolskaja and Wiedemann [49] reported sixteen cases in which six patients were operated on within twenty-four hours from the time of injury; one (16 per cent) died; the other ten were operated on in from forty-eight to 120 hours after injury; 90 per cent of these died. Two hundred and twenty-eight (45 per cent) of 504 cases reported by Packmayr [50] ended fatally. One hundred and fifty-one (90 per cent) of 169 cases of rupture without external wounds ended fatally. In contrast to this, stab wounds or gunshot wounds of the bladder end fatally in only from 22 to 24 per cent of cases.]

Cassuto [51] reported a case in which a fairly large vesical tumor was treated with a high frequency current of about 400 milliamperes. The bladder contained 150 cc. of fluid. During the procedure, a fairly strong explosion occurred in the bladder which even the patient heard, although he did not feel any pain. The bloody contents were removed from the bladder and a retention catheter put in. Slight hematuria occurred for five days without any further untoward symptoms. Cystoscopy eight days later revealed edematous mucous membrane with diffuse furrows spreading over the entire mucous membrane and even extending into the muscular layers.

Bitschai [52] discussed two groups of cases of vesical rupture, one traumatic, the other spontaneous. The former is due to external force. It is rare for the latter to occur, except in cases of disease of the central nervous system from a lesion in the wall of the bladder or the urethra (such as tuberculosis, tumor, hypertrophy of the prostate or stricture).

A case was cited in a man, aged 57, with a history of a former gonorrheal infection. For some time he had had difficult urination with

47. Ullman, E.: Ueber durch Füllung erzeugte Blasenrupturen, Wein. med. Wchnschr. **37**:749, 794 and 823, 1887.

48. Bartels, M.: Die Traumen der Harnblase, Arch. f. klin. Chir. **22**:519 and 715, 1878.

49. Dobrowolskaja, N., and Wiedemann, H.: Zur Frage der intraperitonealen Harnblasenrupturen, Beitr. z. klin. Chir. **89**:700, 1914.

50. Packmayr, O.: Rupture of the Bladder and Its Treatment, Am. J. Urol. **5**:253, 1909.

51. Cassuto, A.: Explosion dans la vessie au cours d'une électro-coagulation, J. d'urol. méd. et chir. **22**:263, 1926; abstr. Ztschr. f. Urol. **21**:393, 1927.

52. Bitschai, J.: Spontanruptur der Blase, Ztschr. f. Urol. **21**:461, 1927.

hematuria. He had severe bronchitis, and was anemic and cachectic; there was 200 cc. of residual bloody urine. Cystoscopic examination revealed marked cystitis and evidence of a malignant tumor in the region of the sphincter. Cystotomy was performed and afforded some relief. A short time afterward, difficulty of urination and dehydration became marked, and the patient died. A diagnosis was made of rupture of the bladder through the malignant area. Necropsy showed diffuse peritonitis. Perforation was found on the upper posterior wall. Musculature was not seen at the site of rupture, nor was there any carcinomatous tissue in this region, the area being replaced by inflammatory connective tissue.

Bitschai stated that while tuberculosis and tumor cause destruction of the vesical wall, in this case the hydrodynamic factors were probably the cause. The tumor caused a valvelike formation leading to the rupture of the atrophied and malnourished vesical wall.

Vesicovaginal Fistula.—Young [53] described a transvesical operation for the repair of vesicovaginal fistula. In one case, eleven operative attempts were made to repair the fistula before it was accomplished by Young. The operation consisted of suprapubic cystostomy, excision of the vesicovaginal fistula from the bladder into the vagina with the assistance of special instruments, resection of the vesical bridge and closure of the fistula in three layers. The first layer was closed by a purse string suture of heavy chromic catgut to approximate the vaginal mucous membrane. A finger was inserted in the vagina and pressure made on the anterior vaginal wall to elevate the vaginal end of the fistulous tract and to expose the mucous membrane. By this means, it was possible to insert the needle parallel to the vaginal wall through the submucosa without penetrating the mucous membrane. The second suture was a purse-string of plain catgut to approximate the vesical muscle. The third was a continuous through-and-through plain catgut suture approximating the vesical mucosa, submucosa and adjacent muscle. The suprapubic wound was drained, the Pezzer catheter being left in place for three weeks. The patient was placed on her abdomen for ten days, after which she was turned on her back. One month after operation, she was dismissed cured.

Young has devised an instrument to aid in elevating the fistulous tract into the bladder; the instrument is similar to his prostatectomy tractor but has delicate nonfenestrated blades. It is introduced into the fistulous tract with the blades closed, then opened and traction made while the tract is dissected out.

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53. Young, H. H.: Repair of Vesicovaginal Fistula; Presentation of a New Instrument, Surg. Gynec. Obst. **45**:226, 1927.

PROSTATE

Hypertrophy.—Randall [54] initiated a discussion on the origin and situation of prostatic hypertrophy citing the work of Tandler and Zuckerkandl, Albarran and Motz. Motz and Perearneau, Lowsley and others, pointed out that there has been a tendency to believe that the hypertrophying prostate consistently originated in only one situation. From a series of 1,218 necropsies, conclusions were drawn that it was impossible to correlate the data with the idea that the hypertrophy invariably originated in any one fixed area. Hypertrophy may originate in any lobe except the true posterior lobe, in which case the data from this series must give definite types of hypertrophy, according to its origin; that is, lateral lobe hypertrophy, hypertrophy in the posterior commissural glandular tissue, hypertrophy in the subcervical gland of Albarran or combinations of any or all should be found. According to Randall, lateral lobe hypertrophy has always been bilateral, although occasionally one lobe may be larger than the other. Specimens were found showing only involvement of the middle lobe, and when this occurred, the hypertrophy of the middle lobe partook of a different contour according to whether the origin was in the posterior commissural tissue or in the subcervical gland of Albarran. In other words there are two glands present anatomically in the median line posteriorly, either of which may undergo hypertrophy independently of the other, or independently of the lateral lobes. These can be recognized through the cystoscope or at operation. The differential diagnosis of these types is made cystoscopically and rectally.

There are differences of surgical procedures according to the presenting type. Preoperative recognition should alter the surgical approach in order to cause the least amount of injury, permit clean enucleation and minimize the probability of postoperative hemorrhage. These factors likewise could not but influence the completeness and permanency of cure and decrease definite postoperative morbidity which has so regularly followed prostatectomy.

When only bilateral hypertrophy is present during the suprapubic operation, each lobe should be separately enucleated; in hypertrophy of the lateral lobes and posterior commissure, enucleation starting about one lobe should follow the line of the false capsule under the posterior commissure and across the median line and the apex of the trigone and thence directly into the line of cleavage and about the opposite lateral lobe, the hypertrophic tissue being removed en masse. If there is hypertrophy of the subcervical glands, it being recognized that these lie without the normal prostatic capsule and are covered only by mucous

54. Randall, Alexander: Commissural Prostatic Hypertrophy, Am. J. Surg. 2:478, 1927.

membrane, such a lobe could be immediately pinched off from its pedicle without further manipulation.

In perineal prostatectomy, the same rules hold true in regard to separate or total adenectomy. During the perineal operation, one should not fail to look for, recognize and remove coexisting subcervical hypertrophic tissue, remembering that it would not be removed from within the capsule and often lies as an intravesical projection free of any attachment to other hypertrophied gland tissue.

As the normal histology presents two masses of gland tissue lying in the median line and presenting so-called middle lobes when hypertrophied, but having separate origin and separate anatomic significance, in the future the term "middle lobe" should be left out and such growths should be spoken of as arising either from hypertrophy of the posterior prostatic commissure or from hypertrophy of the subcervical gland.

[ED. NOTE.—Beer, in discussing Randall's paper, felt that Randall was not entirely sure of middle lobes and commissural hypertrophies, and he himself favored the term "middle lobe." Since there are two commissures at the vesical neck, it only tended to complicate matters. Albarran glandular hypertrophy as a clinical entity is rare; Beer believed it to be less than 2 per cent. Dismissing this type, he felt that his experience had been similar to Randall's, that Zuckerkandl and Tandler were right in their studies that all adenomatous masses developed anterior to the ejaculatory ducts although not always from the middle lobe, and that they were often lateral in origin as well as in the floor of the posterior urethra above the vernmontanum. The posterior lobe becomes compressed against the capsule as adenoma develops in the middle and lateral lobes. Beer felt that it is not so important to know what is to be encountered surgically, yet the picture should be accurate if the approach is perineal; extensive study is not essential for the suprapubic operation, although cystoscopy is usually performed in all cases. The important point to remember from this presentation is that in postmortem studies the commissural adenomas or adenomas of the middle lobe begin much earlier than do those in the lateral lobe; in the sixth decade, the two combined become the typical picture of prostatic obstruction.

Lowsley felt that Randall's paper is a distinct contribution, and he agreed with all the statements. He believed that hypertrophy may begin in any one of the four sections of the prostate; everybody feels certain that it does not occur in the posterior lobe. Lowsley felt that Beer was wrong as to the lack of subcervical gland enlargement. He had found that in 23 per cent of men over 30 years there was more or less enlargement of the subcervical gland. When this growth is small, the patients may wander from physician to physician because of inability to recognize the true condition. They will be found to have subcervical enlargement,

and are seriously affected because they suffer from frequency. Such cases need careful observation. True enlargement of the middle lobe is rare. Before Hinman's modification of the technic of operation Lowsley operated on 40 per cent of his patients suprapubically for the simple reason that when the subcervical gland was involved, the mass could be better removed suprapubically in its entirety. Hinman's modified technic affords better exposure of the prostatic bed and vesical orifice and in most instances it is possible to remove large subcervical masses; he had already removed one about 7 by 5 cm. Lowsley said that it is interesting to have Randall agree so thoroughly to views suggested by himself from the embryologic point of view, and that Tandler had changed his ideas to make them fit the embryology which had been studied more thoroughly since he and Zuckerkandl first studied the prostate. Their studies were accurate, but the embryologic studies of the prostate had made it possible to explain the pathologic conditions much more satisfactorily.

Morton felt that he could not entirely subscribe to Tandler and Zuckerkandl's work, especially in view of the excellent paper of Randall's. Three years ago, he did some work on hypertrophied prostates in Professor Bauer's laboratory in Vienna and could not make the facts fit Tandler and Zuckerkandl's theory. He had found the hypertrophy of tubules and muscular fibers extending entirely through the prostate in all lobes and failed to find the thinned out remains of the original prostate at the periphery. He could not explain these facts at that time, but from Randall's paper he was convinced that the hypertrophic change in the prostate may be universal and not confined to one group of glands, or it may affect one limited portion of the gland.

Morrissey supplemented Randall's paper by showing the specimen of a patient, aged 42, who had suffered from retention for five years and on whom the Young's punch operation had been performed three years previously. He was temporarily relieved by the operation, but three months before Morrissey showed the specimen there was again 40 cc. of residual urine. Young's punch operation was performed without much benefit and the bleeding continued for three months. Perineal prostatectomy was then performed, and a large growth of the posterior lobe was removed. Although it did not correspond to the Albarran type, it had a lamella of its own, separated from the two lateral lobes. The bladder did not empty until this was removed. On the upper surface, there was a small indentation where a piece of fair size had been removed by the Young's punch. Morrissey said that he has not had much success with Young's punch, possibly because the cases were not properly selected. Morrissey has used Braasch's instrument with some success, using the Bumpus method of fulguration of the prostatic area to check bleeding.

Randall, in closing, stated that he used the term "middle lobe" by force of habit, but really meant commissural hypertrophy. He agreed with Lowsley that subcervical hypertrophy was not infrequent; from his statistics it formed 30 per cent of the cases of hypertrophy when occurring alone; combined with bilateral enlargement, the percentage was immediately augmented. Randall wished to emphasize the choice of operation according to type of hypertrophy. He was convinced that definite preoperative pictures could be diagnosed from the clinical, cystoscopic and rectal examinations, which would place each prostatic case in a definite group and would classify it as to the type of hypertrophy; for instance, in the case of sudden complete retention, in which catheter drainage will tide over the acute phase, voluntary urination being reestablished on removal of the catheter and little, if any, residual urine being revealed. In this type there is only bilateral extravesical lobe hypertrophy, which can be proved by both rectal and cystoscopic examination, while at operation two separate lobes will be found and should be separately enucleated. In the second type the patient is in fair health, but when examined a large amount of residual urine is found which preliminary treatment will not influence. In all probability, rectal and cystoscopic examination would reveal the enlargement of the lateral lobe and the hypertrophy in the posterior commissure. The hypertrophied mass should be removed whole and should include both lateral lobes attached to one another by the hypertrophic commissural tissue. In either of these types can suprapubic or perineal prostatectomy be successfully performed, although Randall preferred removal of the commissural enlargements suprapubically and the simple bilateral one perineally. When the subcervical glands become hypertrophied, the best approach is suprapubically because of the anatomic origin of the enlargement and the fact that such lobes are always intrasphincteric as well as intravesical. Randall believed that these are refinements of diagnosis and operative technic which although they are not essential have a decided influence on conservative surgery, minimizing injury, offsetting hemorrhage and giving greater assurance of permanency of cure.

Prostatectomy.—Thomson-Walker [55] believed that the time has come when prostatectomy should do more than save the life of the patient, that it is now necessary to go further and insure functional success as well. Thomson-Walker's mortality in 156 consecutive cases is 4.4 per cent. He believed that causes of failures may be reduced to two fundamental factors, sepsis and obstruction. The belief that all urinary disorders are septic is erroneous and is the result of unsatis-

55. Thomson-Walker, John: Failures of Prostatectomy, Lancet **212**:1009, 1927.

factory surgical methods. The day is past when bladder wounds are encrusted with phosphates and the surrounding skin inflamed and ulcerated. Some of the commoner septic complications are cystitis, epididymitis, seminal vesiculitis, pyelitis and pyelonephritis. Thomson-Walker has found that the number of cases of enlarged prostate in which the bladder has been infected by catheter is much smaller than it was ten or fifteen years ago, but it still amounts to 44 per cent in private practice and 53 per cent in hospitals. He believes that few cases need the two stage operation.

Cholesterol plays an undefined part in the process of immunity, stimulating the production of antibodies. Immunization processes have been shown to be accompanied by a high cholesterol content of the blood; low "blood cholesterol" in a case of acute or chronic retention due to prostatism is significant of low capacity for antibody formation and suggests that the patient is a poor operative risk. The combination of high blood urea and a low cholesterol content is serious. Certain factors, however, such as arteriosclerosis, glycosuria and malignancy, produce a high cholesterol content, and therefore tend to modify its significance. The normal average cholesterol content of the blood is 0.161 per cent and less than 0.130 per cent is abnormal. MacAdam and Shiskin found that sixteen of eighteen patients whose blood cholesterol was less than 0.130 per cent died from pyelonephritis; the other two recovered.

The sources of sepsis are: (1) dislodgement of bacteria into the blood from the rectal wall during enucleation; (2) postoperative tags, shreds and partly detached nodules of prostate glands, capsule, urethra and mucosa, forming centers of sepsis and masses of slough, and (3) postoperative suprapubic wound.

Obstruction following suprapubic prostatectomy varies from slight difficulty in micturition to complete retention with suprapubic fistula. Thomson-Walker has classified these obstructions as follows: (1) fibrous contraction, valvular folds or adenomatous nodules at the vesical neck or in the prostatic lobe, and (2) new growth in the wall of the lobe of the prostate due to recurrence of simple enlargement of the prostate or malignant growth.

[Ed. Note.—Thomson-Walker has been one of the foremost exponents of the suprapubic methods of prostatectomy and has obtained excellent results. In an earlier publication he stated that in ordinary cases without pronounced renal impairment or severe infection, the two stage operation is certainly not safer than the one stage. In the average prepared case, hemorrhage is not more common in the one stage operation, and no advantage need be expected from cystotomy. Two stage operations were performed in only sixty-three (7.6 per cent) of a series of 820 of his cases. The patients had chronic urinary retention, sepsis,

or could be catheterized with difficulty or not at all. He considers the two stage operation an attempt to repair the mistakes of earlier neglect or unskilful treatment. Following prostatectomy, all tags, folds of bladder mucous membrane and semidetached plaques of capsule or nodules of prostate are removed. A hemostatic stitch is introduced on each side of the neck of the cavity, and a continuous suture of fine catgut is put in from the right side around the posterior edge and finished on the left side. If necessary, the capsule is packed with iodoform gauze. Thomson-Walker believed that several factors contribute to the formation of sepsis; one is finger enucleation by rectum.]

Lower [56] stated that operation on the bladder in which drainage must be instituted is never an ideal procedure. For many years, he has closed the bladder after the removal of stones or tumors and has maintained drainage by means of a urethral catheter. Recently he has applied this complete closure following prostatectomy. He has adopted a method whereby the bleeding is entirely controlled by suture, and has discarded the use of packing or of any kind of a distensible bag. He has employed this method in a series of fifty cases, in most of which the bladder was closed at the time of operation. In a few instances, a rubber tube was inserted suprapubically for a few days. A catheter is passed through the urethra. With a dot-and-dash stitch, a suture is then passed from the bottom of the cavity from which the prostate has been removed, along the wall of the cavity up through and including a small margin of the mucous membrane of the bladder. The needle is then removed and rethreaded on the other end of the suture, and the same procedure is carried out on the opposite side. With this suture the walls of the cavity are brought in apposition, snugly but not tightly, and the catgut is cut short. Catgut no. 0, or not heavier than no. 1, is used. The suture is inserted below the catheter, and as many more are applied as may be necessary to close the cavity. All the tag ends of the mucous membrane are trimmed off so that a good approximation can be made, thus facilitating healing and preventing the possibility of a tag dropping into the urethra and causing obstruction. One fine catgut suture is then passed through the catheter to hold it in position.

Since Lower has employed this method of controlling hemorrhage and completely closing the bladder he has found that the period of convalescence is shortened, that postoperative care is lessened, and that the incidence of suprapubic fistula is reduced to a minimum.

Chute, in commenting on Lower's method of bladder closure, said he believed that Lower's success is due to his operative skill, but that

56. Lower, W. E.: Complete Closure of the Bladder Following Prostatectomy; Preliminary Report, J. A. M. A. **89**:749 (Sept. 3) 1927.

the casual operator should continue to use the old method of postoperative suprapubic drainage.

Lewis agreed with Chute. He said:

> It seems to me that the field for this method would be limited, not only because of the need for expertness on the part of the operator, but as related to the patients themselves. In the septic bladder I would hesitate to have it attempted even in the hands of Dr. Lower for they will almost surely open up. I have tried sewing up the bladder following suprapubic operations and discontinued the practice as unsatisfactory and undesirable.

Randall said:

> I think Dr. Chute is correct. Dr. Lower's manual skill at the operating table is equaled only by his artist in depicting the closure. I do not know how often he sees these big gaping wounds, but I think that is not the experience of most of us. I wish to criticize the procedure from several points of view: first, one's ability to observe and place the sutures as he has depicted it; second, the advisability of leaving suture material in such an operative field; third, the question of sewing at all through the thin lamina of tissue with the rectum in such close proximity. Whether he gets primary healing I doubt, but a fourth point could be raised that he is forming an artificial sphincter according to his judgment but not according to nature. These critical points are mostly academic, but there is one thing that all urologists have fought for twenty years, and if everything else was denied us we would hold to it alone, for if there is any one thing that has changed mortality in this type of surgery, that one thing is drainage. We all know what it means in these cases to drain preoperatively, and I think, yes, I positively know, that it will be a great fault to withdraw that drainage postoperatively.

Goldstein,[57] being impressed by the relative frequency of epididymitis after prostatectomy and following the work of Morson, has made a careful study of ligation of the vas deferens prior to prostatectomy.

Bilateral ligation and section of the vas deferens was performed in five one stage, seven two stage, and thirteen perineal prostatectomies as compared with no ligation in eleven one stage, nine two stage and five perineal prostatectomies. In the sixteen one stage prostatectomies in which the vas deferens of eleven cases was not ligated, epididymitis developed in four, while in sixteen cases of two stage prostatectomy in which the vas was ligated in seven and not ligated in nine, epididymitis did not develop. The epididymitis in the five cases without ligation made its appearance in from thirteen to twenty-two days after the original prostatectomy, an average of eighteen days. The complication in the one perineal case in which ligation was performed came on the thirty-fourth day after operation, and after the patient had returned to his home.

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57. Goldstein, A. E.: Bilateral Ligation of the Vas Deferens in Prostatectomy, J. Urol. **17**:25, 1927.

The close association of the development of epididymitis shortly after urination in cases of prostatectomy causes one to suspect a possible focus of infection in the seminal vesicles, as suggested by Boyd and Morson. In all probability, this is secondary to the existing cystitis. In view of the fact that the operative procedure is only increased by from five to ten minutes with the probability of no complicating epididymitis, it appears that the precedure might be rational. Complicating epididymitis in old men who are frequently debilitated and whose resistance is lowered not only delays convalescence but is discouraging to the patient. Sometimes, in the presence of complications, incision and drainage is necessary. In the one case in which epididymitis developed after ligation and section, it occurred five weeks after operation and two weeks after the patient had returned to his home.

Lazarus [58] found that roentgen-ray treatment is distinctly useful in selected cases of hypertrophy of the prostate and prostatitis.

Urinary obstruction in adenoma of the prostate depends to a large extent on the degree of edema of the mucosa of the prostatic urethra. This same congestion and edema of the mucous membrane are significant in prostatitis. The application of the roentgen ray is also often a valuable palliative measure in the treatment of these conditions. Its good effects are dependent on the ability of such irradiation to reduce congestion. Roentgen rays will not sterilize an infected prostatic focus and do not reduce the size of the prostatic tumor.

Davis [59] asserted that the mortality from prostatectomy (properly performed) compares favorably with that of the lesser of the major surgical procedures, and that prostatectomy may therefore be classified among the safe operations. Davis' report includes 107 consecutive cases of perineal prostatectomy with only one death, a mortality rate of less than 1 per cent. While this is a good record, it is not particularly unusual, since larger consecutive series, with lower mortality rates, have been reported by others. Cecil has reported 100 consecutive cases with a mortality of 2 per cent, and Hinman a series of eighty-one operations without a death. Hunt's recent report includes 204 cases with only three deaths, while Young has reported several large series, his largest published number of consecutive cases without a death being 198. Therefore, since large series of cases of prostatectomy, with surprisingly low mortality rates, have been reported by different operators, it is clear that such results may be consistently accomplished by careful effort,

58. Lazarus, J. A.: Deep Roentgen Therapy in Disease of the Prostate Gland, J. Urol. **17**:37, 1927.

59. Davis, Edwin: Perineal Prostatectomy Under Sacral Anesthesia; One Hundred and Seven Consecutive Cases with One Death, J. A. M. A. **88**:784 (March 12) 1927.

and are not due to good fortune alone or to mere chance. In this connection it is of interest to recall that prostatectomy has not always been the mild procedure that it is today. To quote from Young, "Twenty years ago, the general mortality from prostatectomy was greater than 20 per cent; now it is almost nil." The lowering of this mortality rate is dependent on four factors: (1) the general recognition by the medical profession of the value of preoperative drainage; (2) the growing enlightenment of the public, with consequent knowledge of the increased danger of delay; (3) the increasing popularity of sacral anesthesia, and (4) more careful attention to hemostasis.

Of these four factors, the first is by far the most important. There is unquestionably a lurking danger in attempting immediate prostatectomy; the figures of Hunt clearly show this. In analyzing a series of 1,783 cases of prostatectomy he divides these into three groups: (1) poor risks (preliminary suprapubic drainage) 437, mortality 7.5 per cent; (2) average risks (preliminary catheter drainage) 680, mortality 3.2 per cent, and (3) good risks (without preliminary drainage) 666, mortality 6.6 per cent.

Hunt stated in regard to the relative value of the perineal and suprapubic routes that an unprejudiced analysis of the ultimate functional results and mortality rates following both methods of operation by those experienced in them shows that these indexes of merit can no longer be utilized to discredit one or the other method.

Only one of Davis' patients died in 107 consecutive cases of perineal prostatectomy. One of the cases was persistent perineal fistula. There were no cases of complete incontinence and only three in which the control of urine was not satisfactory. The average age of the patients was 69. There were fifty-three patients more than 70 and ten more than 80.

[Ed. Note.—As Davis stated, sacral anesthesia is the ideal anesthetic for perineal prostatectomy. After a single caudal injection the maximal point of anesthesia is found to be almost identical to the point of perineal attack. Sacral anesthesia is also an important factor in lowering the mortality rate in suprapubic operations, but due to the greater operative field more extensive anesthesia is required, usually complete sacral block as well as suprapubic block; this injection requires much more skill than the caudal injection and consequently is not used outside of the large clinics as frequently as results warrant. Sacral anesthesia also unquestionably lowers the mortality in the suprapubic operation. The following table shows the mortality in a series of 526 cases from the Mayo Clinic in which operation was performed during a three-year period. This series indicates the desirability of sacral anesthesia over spinal or ether anesthesia.

In cases of suprapubic prostatectomy, there was no difference in the late results following the different types of anesthesia. Sacral anesthesia does not entirely eliminate the possibility of respiratory infection, which, when it occurs following the administration of ether, is usually attributed to pulmonary irritation from the anesthetic. Sacral anesthesia definitely eliminates the group of immediate deaths usually attributed to shock and cardiac disease. The earliest death in the series of 270 cases occurred on the fifth day and followed postoperative hemorrhage and urinary infection; one death on the eighth day was due to uremia, and the remaining seven deaths, in the cases in which sacral anesthesia was employed, occurred from thirteen to forty days postoperatively, but in no case was there a definite causal relationship between the sacral anesthesia and death.

In either the perineal or the suprapubic operation, the most important factors are the preliminary preparation and complete surgical hemostasis; the method of surgical approach is of less importance.

Cases from the Mayo Clinic

			Hospital Mortality	
	Cases	Percentage	Cases	Percentage
Sacral	270	51.33	9	3.33
Spinal	187	35.55	13	6.95
Ether	69	13.12	5	7.24
Total	526	....	27	...

Thomson-Walker [60] reported a case of recurrence of enlarged prostate after prostatectomy. The first operation was performed in 1916. The patient's convalescence was uneventful, and he remained free from pain for eight years, when epididymitis with frequent micturition and difficulty occurred. When rectal examination was made, the swelling felt like an ordinary, moderate sized enlargement of the prostate gland. There was obstruction to a catheter at the internal meatus.

Ten years after the first operation, Thomson-Walker opened the bladder and found a prostatic nodule about the "size of a cherry" projecting into the bladder at the posterior lip of the internal meatus. Partly by dissection and partly by enucleation, a structure similar to an enlarged prostate gland was removed, and the patient was treated as for ordinary open prostatectomy. The specimen, viewed from the posterior aspect, resembled the enucleated specimen of an ordinary enlarged prostate. Seen from the anterior aspect the ring at the internal meatus was complete, but below this the ring was incomplete, and there was a wide tunnel representing the prostatic urethra, which would admit

60. Thomson-Walker, John: Recurrence of Enlarged Prostate After Prostatectomy, Proc. Roy. Soc. Med., Sect. Urol. **20**:20, 1927.

the forefinger and was wider below than above. The lining of this tunnel was smooth and there were numerous small openings, apparently the ducts of glands, in the wall.

The microscopic section showed an appearance like that of an ordinary enlarged prostate gland, namely, gland tubules in groups, dilated and embedded in unstriped muscle and fibrous and elastic tissue.

MacDonald [61] reported the case of a man, aged 68, similar to the case of Thomson-Walker, in which prostatectomy had been performed for an adenomatous enlargement of the gland. A second operation was performed because of hematuria and an adenomatous prostate was removed completely.

[Ed. Note.—A number of similar cases of recurrent prostatic enlargement have been reported. Most operations were performed before the technic had reached its present state of precision. In some cases, recurrence of the enlargement was due to incomplete removal of the gland at the first operation. Thomson-Walker performed both the operations in his reported case; a recurrence following prostatectomy by such a skillful operator suggests that true reformation of the gland may occur.]

URETHRA

Tuberculosis.—Wiedhopf [62] reviewed the literature and reported a case of his own. Tuberculosis of the female urethra is exceedingly rare. Von Krzyuricki, in 1,246 necropsies from the Dresden Sanatorium, found tuberculous involvement of the various organs in 40 per cent of cases; of these, 5 per cent were urogenital (twenty-nine cases, fifteen men and fourteen women). In only one woman was the urethra affected. Von Pavel gave a similar report of necropsy material from the Breslau Pathologic Institute. The urogenital system was involved in 40 per cent of 1,455 cases of tuberculosis. The urethra was involved in only seven cases, all in men. Schlimpert performed 8,084 necropsies at the Institute of Schmorl; 3,514 (61 per cent) of the subjects were women. Pulmonary tuberculosis was present in 84.3 per cent of these, and urogenital infections in 1.4 per cent; in only one case was the urethra involved. In 1892, Aherns reviewed four cases. Wiedhopf cited a case in a woman, aged 58. Polyps were seen projecting from the meatus. The patient could not be catheterized because of an obstruction by polyps 1 cm. from the meatus. At operation, 1 cm. of the urethra was resected after which the patient could be readily

61. MacDonald, S. G.: Prostatic Enlargement Following Prostatectomy, Proc. Roy. Soc. Med., Sect. Urol. **20**:18, 1927.

62. Wiedhopf, O.: Strikturierende Tuberkulose der weiblichen Harnröhre unter dem klinischen Bilde eines urethralen Polypen, Ztschr. f. Urol. **21**:352, 1927.

catheterized. Convalescence was uneventful. Pathologic examination of the removed tissue showed tubercles just beneath the mucous membrane. Careful study of the kidney revealed closed right pyonephrosis, in all probability tuberculous, which in turn had infected the urethra.

Wiedhopf believed that the rarity of this condition in women is due to the fact that only urine passes through the urethra; in men the frequently infected genital secretions also pass. The shortness of the urethra in women may also be a factor. The infection is usually from the kidney or peripheral urinary tract rather than from such a condition as lupus of the vulva.

Tumors.—Schmidt [63] found only seventeen cases of sarcoma of the female urethra in the literature. He described a case of tumor in the urethral wall about 2 cm. in diameter. This type of sarcoma, which originates in the musculature of the urethra and includes the adjacent connective tissue and vessels, extends in the loose periurethral connective tissue anteriorly to the meatus. Following destruction of the musculature, the urethral lumen is invaded. The treatment of urethral sarcoma is operative. It may be removed, as in Schmidt's case, with the Paquelin cautery. Wide resection is not necessary, since the postoperative prophylactic use of the roentgen ray is productive of good results.

[Ed. Note.—Sarcomas similar to connective tissue tumors in other parts of the body are most common in young persons. They may be pedunculated, and in the female often protrude from the urethra. They grow rapidly, metastasize extensively, and the prognosis is poor. Mariachess [64] reported a case of a man, aged 22, in whose penis was a mass which increased rapidly in size; four months after the onset, the growth caused complete obstruction. Mark [65] observed a case in a man, aged 24. The growth was in the anterior urethra and caused severe dysuria and terminal hematuria. Several months later, the whole urethra was involved. Kaufmann [66] reported a case of spindle cell sarcoma occurring in a man, aged 55. Albrecht [67] reported a case of pigmented sarcoma in a man; the condition was discovered at necropsy.

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63. Schmidt, H. R.: Spindelzellensarkom der weiblichen Urethra, Zentralbl. f. Gynäk. **1**:3122, 1926; abstr. Ztschr. f. Urol. **21**:390, 1927.

64. Mariachess, J.: Sarcome de l'uretère. Émasculation totale, Ann. d. mal. Org. Gén.-Urin. **16**:886, 1898.

65. Mark, E. G.: Primary Sarcoma of the Male Urethra; Report of a Case, Tr. Am. Urol. A. **5**:59 and 73, 1911.

66. Kaufmann, C.: Verletzungen und Krankheiten der männlichen Harnröhre und des Penis, F. Enke, 1886, p. 331.

67. Albrecht, H.: Ein Naevus papillaris pigmentosus der Pars prostatica der Urethra mit sarko-karzinomatösen Metastasen, Verhandl. d. deutsch. path. Gesellsch. **14**:253, 1910.

TESTICLE AND EPIDIDYMIS

Hydrocele.—Campbell [68] reported a series of 502 cases of hydrocele. He stated that infection and trauma are the chief known causes. Probably painless subacute epididymitis is the underlying factor in many cases. The condition is most common in young adults; in infancy it is usually congenital and associated with hernia. While simple tapping gives relief in many cases, open operation, preferably excision and eversion of the sac, is the procedure of choice. Local anesthesia is most satisfactory in these cases. A hemostatic scrotal compression bandage which is of great service following operation is described.

Simple eversion (bottle operation) is useful in small hydroceles without thickened sacs. In all but seven cases the excision and eversion operation was employed. The mass is delivered through a scrotal incision and incised from end to end. The redundant vaginalis is excised, complete hemostatis is obtained, a running suture being taken in the vaginalis if necessary, and the remaining edges everted and sutured behind the cord. The testicle is replaced in the scrotum, and the skin is closed without drainage. A small gauze dressing is applied, over which is placed the compression bandage; this consists of a four-tailed adhesive bandage which affords support to and, more particularly, compression of the scrotum. The average period in the hospital in all uninfected cases was six and one-tenth days. Many patients were out of the hospital on the fifth day.

Statistics studied from a large number of operators have been compiled by Bruns. When aspiration and injection was performed, the recurrence was 6.1 per cent in 1,593 cases. In 1,216 cases in which open operation was performed relapse occurred in thirty (2.4 per cent).

URACHUS

Tumors.—Brady [69] reported a case of solid tumor of the urachus in a woman, aged 43. These tumors are closely allied to tumors of the dome of the bladder and unquestionably are sometimes confused with such tumors. There have been reports, including Brady's series of twenty cases, of solid tumors arising from the urachus. The average age of the patients was 44. The youngest patient was a boy, aged 11, with a primary sarcoma of the urachal sheath; the oldest was a man, aged 82, with an adenocarcinoma of the urachus and secondary involvement of the bladder. These tumors have been found more frequently in men than in women. In this series, the sex of the patients was not recorded in three cases; in three the patients were women, in fourteen men.

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68. Campbell, M. F.: Hydrocele of the Tunica Vaginalis, Surg. Gynec. Obst. **45**:192, 1927.

69. Brady, Leo: Solid Tumors of the Urachus, Arch. Surg. **14**:46 (Jan.) 1927.

These tumors have caused the following symptoms: pain in the middle and lower part of the abdomen and, when the bladder was involved, dysuria, polyuria and hematuria. Four patients discovered lumps in the abdominal wall before they experienced any trouble from them. Nuboer's case was unique in that his patient complained of pain in the left arm and due to distant metastasis before the primary growth had been noticed or had given any symptoms.

Eighteen of the reported cases were malignant; two were benign. In nineteen cases, the growths arose primarily in the urachus. In one case, a primary papillary adenocarcinoma of the bladder extended to, and secondarily involved, the urachus which was patent. In fourteen of the eighteen cases, the bladder had already been invaded by the growth when the patient consulted a physician. Whenever this had occurred, there was a broad band of induration extending from the lower pole of the tumor to the vertex of the bladder at the point where the median abdominal ligament (the remains of the urachus) joins that organ. In six instances only were the outer coats of the bladder involved; in eight, cystoscopic examination showed carcinomatous masses projecting from the vertex into the cavity of the bladder.

In only four cases of malignant urachal tumors was the peritoneal cavity found to have been invaded by the growth. Radical operation was performed in twelve of the malignant cases. In seven cases in which radical excision of the malignant tumor was carried out the vertex of the bladder was removed. Eight patients recovered satisfactorily.

Brady's study of malignant urachal tumors has impressed him with the fact that these growths occur more frequently than had previously been supposed, and that in order to expect cure radical operation must be performed, usually including removal of the vertex of the bladder and portions of the anterior abdominal wall.

[Ed. Note.—It is difficult to distinguish definitely between tumors of the umbilicus and those of the upper portion of the urachal tube; a similar difficulty is encountered in differentiating tumors of the lower urachus and those originating in the dome of the bladder. Barringer reported an unusual adenocarcinoma involving only the apex of the bladder; the larger part of the tumor was above the bladder. Ewing, who examined the tumor, said that the growth was unique and probably came from a remnant of the allantoic end of the bladder, or possibly from a cloacal inclusion. The urachus ordinarily becomes obliterated at about the third month of fetal life. It becomes obliterated irregularly so that, at times, segments occur in which the lumen persists. Rankin stated that these unobliterated segments form cavities that may later give rise to the urachal cysts which are seen clinically. The lining of the urachal tube is composed of one or more layers of transitional epithelium, much like the mucous membrane of the bladder.]

ANESTHESIA

Lower [70] stated that in the field of genito-urinary surgery it has been found that general inhalation anesthesia is not the anesthesia of choice, since in most cases there is either functional impairment or some pathologic condition of the kidney. Lower deprecated the application of any one method of administering anesthesia to the exclusion of others and proposed that the anesthetic be applied strictly according to the patient, that is, that it be adapted to the psychic and physical condition of the patient as well as to the anatomic possibilities of the case.

The anesthetic chosen in genito-urinary surgery and the method of administration must be one of the following: nitrous oxide-oxygen analgesia, ethylene gas anesthesia, spinal anesthesia, sacral anesthesia and local anesthesia. In analgesia produced by nitrous oxide-oxygen, a sufficient degree of relaxation is rarely obtained. While nitrous oxide-oxygen analgesia may be used as an adjuvant, some other method of anesthesia is required; therefore, the choice is further reduced to spinal, sacral or local anesthesia.

Lower believed that spinal anesthesia is more hazardous because of its effect on blood pressure. He placed his chief reliance on sacral block and local infiltration for suprapubic and scrotal operations, and on regional nerve block, local infiltration and nitrous oxide-oxygen analgesia for operation on the kidney.

In operations on the prostate and bladder, sacral block is employed. A 1 per cent solution of procaine hydrochloride combined with 6 minims of a 1: 1,000 solution of epinephrine is injected through the sacrococcygeal membrane into the caudal canal, the insertion of the needle being preceded by progressive anesthetization of the path to the caudal canal. Occasionally this is followed by injections through the second, third and fourth sacral foramina on each side. After these injections have been made, the patient is turned over and a complete regional block of the abdominal wall is made. The anesthesia obtained by this method lasts for an hour or more, complete relaxation is secured, and the operation is painless.

If the operative field includes the bladder, the wall of the bladder is infiltrated with 0.75 per cent solution of procaine hydrochloride. If the prostate is to be removed, the procaine is infiltrated between the gland and the capsule, as this helps to separate the prostate from the capsule. Sacral anesthesia, therefore, is of value in all operations on the bladder and prostate, as removal of a diverticulum of the bladder, removal of bladder stone, resection of the bladder, and prostatectomy. If the patient is apprehensive, the anesthetist is prepared to administer nitrous oxide-oxygen until the stage of analgesia is reached.

70. Lower, W. E.: Anesthesia in Genito-Urinary Operations, Ann. Surg. **86**:268, 1927.

URINARY INFECTION

Ball [71] believed that adhesion and anatomic proximity of inflammatory lesions of the intestinal tract and the pelvic viscera are responsible for many cases of urinary infection. In reviewing a series of cases, he found that in almost every instance it was the onset of an acute flare-up of an intestinal or pelvic lesion during the course of chronic urinary infection that led to the discovery of the actual cause of the trouble.

Adhesion of a chronic lesion, or obstruction caused by an acute lesion of the alimentary tract or pelvic viscera, to the ureter, may be of such a nature that, although not obliterating the lumen of the latter, it may act in such a manner as to cause dilatation of the renal pelvis and congestion of the renal cortex, and thus provide a condition amenable to the persistence or recurrence of an infection. Ball does not intend to suggest that direct contact of the urinary passages with infective lesions of the adjacent structures is the only channel through which these infections take place, but he hopes rather to stimulate investigations in this direction with a view to explaining some of the cases of urinary infection for which the explanations now in use are inadequate.

URINARY PIGMENTATION

Poole [72] reported an unusual condition of pigmentation of the urine following the ingestion of red beets (beta vulgaris) and which might readily be confused with other more serious conditions in which red pigment appears in the urine. A boy, aged 6, was admitted to hospital because of periodic reddish discoloration of the urine, failure to gain weight and attacks of abdominal pain. He had had scarlet fever with complicating nephritis. On five occasions following this, reddish urine was noted and the patient never seemed well. Each time he was thought to have had nephritis he had been put on a milk diet, and the red color had disappeared. General examination revealed a malnourished child with choreiform movements, a loud systolic heart murmur and secondary anemia. The urine was deep red but there was no blood, pus or other abnormal constituents. Spectroscopic examination did not show blood pigment and an acid solution did not show the characteristic bands of hematoporphyrin. Beets were removed from the child's diet, and the urine became clear. On the addition of beets to the diet, the phenomenon could be reproduced.

The red color of the urine changed to deep yellow on the addition of alkali, such as potassium hydroxide, and returned on acidification

71. Ball, W. G.: Some Anatomical Factors in Urinary Infections, Proc. Roy. Soc. Med., Sect. Urol. **20**:1, 1927.

72. Poole, M. W.: Anthocyaninuria, Am. J. Dis. Child. **33**:784 (May) 1927.

with hydrochloric or acetic acid. Aqueous solutions of beet juice reacted in a similar way to acid and alkali.

Poole stated that the color of beets undoubtedly is caused by anthocyanin which changes to yellow under certain conditions, the absorption bands of this yellow pigment being identical in position to carotin.

In this case, the presence of the dye in the urine probably was the result of change in permeability of the kidney from injury by nephritis (scarlet fever), since it had not appeared prior to that time.

INDIGOCARMINE FUNCTIONAL TESTS

Wassileff [73] has noted complicating reactions in four of 279 cases of intravenous injection of indigo carmine. Immediately following the injection there were vasomotor reactions. Shortness of breath, difficulty in swallowing, urticarial eruption, cardiac palpitation and a feeling of anxiety were manifested. In one case there was anuria for forty minutes. In the remaining cases, the symptoms disappeared in ten minutes leaving only a feeling of exhaustion. In one case, however, symptoms lasted for eleven hours.

Wassileff concluded that these reactions are not due to the toxicity of the drug, but rather to dilution of the blood which can be brought about by the intravenous injection of any drug. These phenomena are the expression of a reaction of the organism to the introduction of a foreign body.

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73. Wassileff, I.: Komplikationen bei intravenösen Injektionen von Indigokarmin, Ztschr. f. Urol. **11**:376, 1927.

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